#21

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Applicant	:	Dolors Fernandez FORNER et al.	)
Patent No	:	5,565,447	)
Issued	:	October 15,1996	)
Filing Date	:	May 9, 1995	) **BOX PATENT TERM EXTENSION**
For	:	NEW INDOL DERIVATIVES	)
Atty. Dkt.	:	31767-138142	)

July 3, 2001

Assistant Commissioner for Patents
Washington, D.C. 22031

Sir:

TRANSMITTAL OF AN APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM (IN TRIPLICATE) of the above-identified patent for a product approved on May 7, 2001.

The requisite fee of $1120 is attached as a check. Should the fee be missing or should additional fees be due, please charge the same to DEPOSIT ACCOUNT 22-0261 and advise us accordingly.

Respectfully submitted,

Date: July 3 2001

Marina V. Schneller
Registration No. 26,032
VENABLE
Post Office Box 34385
Washington, D.C. 20043-9998
Telephone: (202) 962-4800
Facsimile: (202) 962-8300

DC2/292762

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Applicant	:	Dolors Fernandez FORNER et al.	)
Patent No.	:	5,565,447	)
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July 3, 2001

Assistant Commissioner for Patents
Washington, D.C. 22031

Sir:

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

In accordance with 37 CFR 1.740 (b), **this paper is filed in triplicate.**

This is an application for extension of patent term in writing to the Commissioner pursuant to 35 USC 156 and 37 CFR 1.740. It is made by Almirall Prodesfarma S.A., a corporation organized under the laws of Spain and assignee of the above-identified patent, through the undersigned.

The chain of title to the above-identified U.S. Patent 5,565,447 is set out in Exhibit 1, which includes copies of the relevant recorded documents.

The following information is submitted in accordance with 35 U.S.C. 156(d) and 37 CFR 1.740 and 1.741. The formal requirements of 37 CFR 1.740 are specifically set out below in accordance with the numerical format set forth therein and underlined.

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics;

The approved product is AXERT™ (almotriptan malate) tablets for oral administration. The approved product is almotriptan malate. It is characterized by the following structural formula:

It bears the chemical name: 1-[[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]methyl]sulfonyl]pyrrolidine (±) – hydroxybutane dioate

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred;

The regulatory review occurred under Section 505(b) of the Federal Food, Drug and Cosmetic Act ("FFDCA") and title 21 of the Code of Federal Regulations (CFR).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred;

The approved product was approved by the Food and Drug Administration ("FDA") for commercial marketing pursuant to Section 505(b) of the FFDCA on May 7, 2001. **A copy of the letter from the FDA dated May 7, 2201 setting forth approval of the product is provided in the attached Exhibit 2.**

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients) the use for which it was approved, and the provision of law under which it was approved.

In AXERT, almotriptan malate is the only active ingredient which has not been previously approved for commercial marketing or use under any of the Acts set forth above or any other provision of law. For additional information on the approved product, please see the copy of the Information Brochure attached hereto as Exhibit 3 and paragraph (1) above.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § l.720(f) and an identification of the date of the last day on which the application could be submitted;

The product was approved for commercial marketing on May 7, 2001. The last business day within the sixty-day period permitted for submission of an application for extension of the patent is July 5, 2001. This application is being filed on July 3, 2001; and, therefore, it has been timely submitted.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration;

U.S. Patent: 5,565,447

Inventors: Dolors Fernandez FORNER et al.

Issue Date: October 15, 1996

Expiration Date: October 15, 2013

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings;

A copy of the patent is attached hereto as Exhibit 4.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent;

Attached as Exhibit 5 is a Certificate of Correction totaling 1 page. Attached as Exhibit 6 is a document from the U.S. Patent and Trademark Office, which shows that the first maintenance fee was paid.

No disclaimer was filed and no request for reexamination has been filed.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

U.S. Patent has 6 claims.

Claims 1 and 2 are generic compound claims and each reads on the active ingredient of the approved product.

Claim 3 is a claim reciting three compounds and the hydrochloride salts thereof.

Claim 4 is directed to a pharmaceutical composition, while claims 5 and 6 are method of use claims; all of claims 4-6 require the compounds of claim 1 in the pharmaceutical composition [of claim 4] or as the compound administered [claims 5 and 6].

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) Filed on July 30, 1997, the effective date of the investigational new drug (IND) application is August 29, 1997 and the IND number is 53854; on March 25, 1998, ownership of IND 53854 was transferred from the assignee of the U.S. Patent 5, 565,447 Almirall Prodesfarma S.A. (APF) to Pharmacia and UpJohn (P and U);

(B) On December 20, 1999, a new drug application (NDA) or a Product License Application (PLA) was initially submitted and is designated NDA 20-001; and

(C) The date on which the NDA was approved was May 7, 2001.

The above dates are verified by the documents attached as exhibits, designated by the respective Exhibit numbers (Exhibits 1-7) discussed above and in sections below.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities;

The regulatory activities undertaken to obtain FDA approval of AXERT™ Tablets commenced with the submission of an Investigational New Drug Application (IND 53854 to study the use of AXERT™ in the treatment of migraine. Effective June 16, 1998, clinical studies under IND 53854 were permitted to commence with the removal of a clinical hold.

With the December 20, 1999 submission of NDA for AXERT™, the testing phase ended and the approval phase of the regulatory review period began. Many significant regulatory activities occurred during the approval phase, including meetings with FDA, timely responses to FDA requests for information, amendments, and revised draft labeling.

The regulatory review period for AXERT™ ended with permission for commercial marketing being granted by the FDA on May 7, 2001. All regulatory activities were carried out in a prompt, timely manner in accordance with all applicable statutes and regulations.

Evidence of the numerous and continuous activities which occurred under IND 53854 is provided as Exhibit 7 which comprises a tabulation setting forth key events occurring during the testing phase and the approval phase, and a chronological listing on a daily basis of actions taken and contacts with the FDA. Exhibit 7 is divided into part as follows;

It is readily apparent from Exhibit 7 that the activities were numerous and ongoing continuously reflecting the diligent pursuit of FDA approval of NDA 20-001.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined;

Section 156 (a) contains five prerequisites to extension. As described below by corresponding number each of elements (1) through (5) [listed in the statute] has been satisfied.

(1) The term of U.S. No. 5,565,447 expires October 15, 2013 based on a term which is 17 years from the date of issuance. Therefore, this application for term extension has been submitted before the expiration of the patent term.

(2) The term of U.S. No. 5,565,447 has not been extended heretofore.

(3) This application is submitted by the owner of record of U.S. No. 5,565,447 through undersigned counsel. This application further complies with the provisions of 35 USC 156 (d) in that is submitted with in the sixty day period beginning on the date the product was approved for marketing under the FFDCA, and contains the information required under 35 USC 156(d).

(4) As evidenced by the letter dated May 7, 2001, from the FDA [Exhibit 2] the approved product was subject to a regulatory review period under Section 505(b) of the FFDCA before its commercial marketing or use.

(5) The permission for commercial marketing of AXERT™ after regulatory review under Section 505b of the FFDCA is the first permitted commercial marketing of almotriptan malate. This is confirmed by the absence of any approved new drug application under which AXERT™ could be commercially marketed prior to May 7, 2001 [date of approval].

(6) Statement as to length of extension claimed;

(7) The term of U.S. No. 5,565,447 should be extended by 569 days. The term of extension was determined as follows using the following tabulation:

1. The number of days for the testing phase as defined in 37 CFR 1.775(c)(1)	843
2. The number of days for the approval phase as defined in 37 CFR 1.75(c)(2)	504
3. Total of line 1 and 2	1347
4. The number of days of the period of line 2 which occurred prior to the issue date of the patent	0
5. The number of days of the period of line 2 during which the Applicant failed to act with due diligence as defined in 37 CFR 1.775 (d)(1)(ii)	0
6. Total of line 4 and line 5	0
7. Total of line 3 less the amount of line 6	1347

8. The number of days of the period of line 1 which occurred prior to the issue date of the patent	0
9. The number of days of the period of line 1 during which the Applicant failed to act with due diligence as defined in 37 CFR 1.775(d)(1)(ii)	0
10. The total of line 8 and line 9	0
11. Total of line 7 less the amount of line 10	1347
12. The number of days from line 1	843
13. The number of days from line 10	0
14. The total from line 12 less the amount of line 13	843
15. One half of line 14	421.5
16. The total from line 11 less the amount from line 15	926
17. The original expiration date of the patent	October 15, 2013
18. The Expiration date of the patent if extended by the number of days on line 16	April 28, 2016
19. Date of the FDA final approval	May 7, 2001
20. Limitation set forth in 37 CFR 1.775(d)(3)	May 7, 2015
21. 14 years added to the date on line 19 gives a revised date of	May 7, 2015
22. Earlier of the dates of line 18 or line 21	May 7, 2015
23. Original expiration date of patent	October 15, 2013
24. The patent issued after 09/24/84	12 years
25. The number of years on line 24 added to the date on line 23	October 15, 2025
26. The earlier of the dates appearing on line 22 or line 25	May 7, 2015
27. The original expiration date of the patent	October 15, 2013
28. The number of days by which line 26 and line 27 differ	569

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see § 1.765);

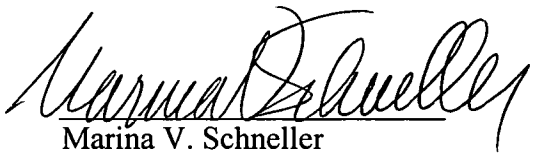
(14) The prescribed fee for receiving and acting upon the application for extension (see § 1.20(j)) is enclosed; and

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Marina Velentgas Schneller
VENABLE
1201 New York Avenue, N.W., Suite 1000
Washington, D.C. 20005-3917
Telephone: (202) 962-4800
Telefax: (202) 962-8300

(b) This application is being filed in triplicate.

Respectfully submitted,



Marina V. Schneller
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Venable
Post Office Box 34385
Washington, D.C. 20043-9998
Telephone: (202) 962-4800
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#292762

MVSJ 2 Exhibit 1

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

31767 138141

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AUGUST 08, 2000

PTAS

VENABLE
MARINA V. SCHNELLER
P.O. BOX 34385
WASHINGTON, DC 20043-9998

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 05/26/2000

REEL/FRAME: 010848/0207
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR''S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
GRUPO PLAFIN, S.A. (FORMERLY KNOWN AS GRUPO FARMACEUTICO ALMIRALL, S.A., FORMERLY KNOWN AS LABORATORIOS ALMIRALL, S.A.) A SPANISH BODY CORPORATE.

DOC DATE: 03/16/1999

RECEIVED
NOV 30 2001
OFFICE OF PETITIONS
DEPUTY A/C PATENTS

ASSIGNEE:
ALMIRALL PRODESFARMA, S.A., A SPANISH BODY CORPORATE
RONDA DEL GENERAL MITRE, 151
08022 BARCELONA, SPAIN

SERIAL NUMBER: 07743388
PATENT NUMBER: 5223504

FILING DATE: 08/16/1991
ISSUE DATE: 06/29/1993

SERIAL NUMBER: 08437682
PATENT NUMBER: 5565447

FILING DATE: 05/09/1995
ISSUE DATE: 10/15/1996

RECEIVED
AUG 17 2000
VENABLE
WASHINGTON DC

PAULA MCCRAY, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

06-19-2000

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MRD
5.26.00

TO THE COMMISSIONER OF
PATENTS AND TRADEMARKS
WASHINGTON, D.C. 20231

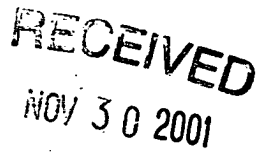
Attorney Reference: 31767-138141 and 31767-138142

BOX ASSIGNMENT

REQUEST FOR RECORDING AND COVER SHEET UNDER 37 C.F.R. 3.28 AND 3.31
Please record the attached original document(s) or copy(ies) thereof.

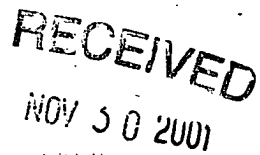
1. Name of party conveying the interest:
GRUPO PLAFIN, S.A. (formerly known as GRUPO FARMACÉUTICO ALMIRALL, S.A., formerly known as LABORATORIOS ALMIRALL, S.A.) a Spanish body corporate.

2. Name and address of party receiving the interest:
ALMIRALL PRODESFARMA, S.A., a Spanish body corporate, of
Ronda del General Mitre, 151
08022 Barcelona, SPAIN



3. Description of the interest conveyed or transaction to be recorded:
[X] Assignment [ ] Other:

4. Application Number:
Patent Number: 5,223,504 and 5,565,447
Registration Number:
[ ] Document filed together with a patent application executed on
_____.



5. Address correspondence concerning this request to: VENABLE Attorneys, P.O. Box 34385, Washington, D.C. 20043-9998.

6. Number of Applications, Patents or Registrations and total fee:
Patents: 2 patent rights @ $40 Total: $80.00
or-
Trademarks: First trademark right $40
___ additional trademark rights @ $25 $____ Total: $_____
If no fee is attached, or if a greater or lesser fee is required, please charge or credit our Account No. 19-3700.

7. Date of execution of document: March 16, 1999.

8. If document is an assignment of a trademark right to an assignee who is not domiciled in the United States, such assignee has designated a domestic representative [ ] per attached designation [ ] other:

9. To the best of knowledge and belief of the undersigned, the foregoing information is true and correct and any attached copy is a true copy of the original document.

10. Date: May 26, 2000

Marina V. Schneller

Registration Number: 26,032

6/2000 JSHABAZZ 00000083 5223504
C:581 80.00 OP

2#135948v1

2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-001

Pharmacia and Upjohn Co.
Attn: Marcia Rogers
7000 Portage Road
Kalamazoo, MI 49001

Dear Ms. Rogers:

Please refer to your new drug application (NDA) dated December 17, 1999, received December 20, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Axert (almotriptan malate) tablets.

We acknowledge receipt of your submissions dated January 5, 2001, January 23, 2001, March 6, 2001, March 13, 2001, March 28, 2001, April 9, 2001 and April 30, 2001. Your submission of March 6, 2001 constituted a complete response to our December 20, 2000 action letter.

This new drug application provides for the use of Axert (almotriptan malate) tablets for the acute treatment of migraine.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-001." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified. In order that we may complete the methods validation process in an orderly fashion, please submit a corrected methods validation package. The necessary corrections were detailed in our fax of May 4, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We note your March 28, 2001 submission includes your Pediatric Development Plan and Proposed Pediatric Study Request. That submission remains under review. We are deferring submission of your pediatric studies until approximately 2 years after approval.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Lana Chen, R.Ph., Regulatory Management Officer, at (301) 594-5529.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

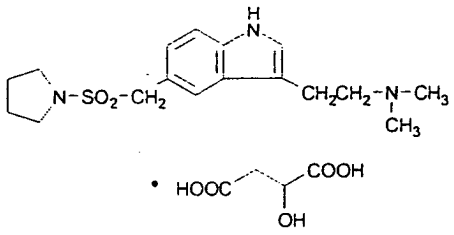
/s/

Robert Temple
5/7/01 05:02:11 PM

NDA 21-001
AXERT™ Tablets
Package Insert
5/4/01

DESCRIPTION

AXERT Tablets contain almotriptan malate, a selective 5-hydroxytryptamine$_{1B/1D}$ (5-HT$_{1B/1D}$) receptor agonist. Almotriptan malate is chemically designated as 1-[[[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]methyl]sulfonyl]pyrrolidine (±)-hydroxybutanedioate (1:1), and its structural formula is:



Its empirical formula is $C_{17}H_{25}N_3O_2S$-$C_4H_6O_5$, representing a molecular weight of 469.56. Almotriptan is a white to slightly yellow crystalline powder that is soluble in water. AXERT Tablets for oral administration contain almotriptan malate equivalent to 6.25 or 12.5 mg of almotriptan. Each compressed tablet contains the following inactive ingredients: mannitol, cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, titanium dioxide, hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol, iron oxide (6.25 mg only), FD&C Blue No. 2 (12.5 mg only), and carnauba wax.

CLINICAL PHARMACOLOGY

Mechanism of Action: Almotriptan binds with high affinity to 5-HT$_{1D}$, 5-HT$_{1B}$, and 5-HT$_{1F}$ receptors. Almotriptan has weak affinity for 5-HT$_{1A}$ and 5-HT$_7$ receptors, but has no significant affinity or pharmacological activity at 5-HT$_2$, 5-HT$_3$, 5-HT$_4$, 5-HT$_6$; alpha or beta adrenergic; adenosine (A_1, A_2); angiotensin (AT_1, AT_2); dopamine (D_1, D_2); endothelin (ET_A, ET_B); or tachykinin (NK_1, NK_2, NK_3) binding sites.

Current theories on the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and pro-inflammatory peptides from sensory nerve endings in an activated trigeminal system. The therapeutic activity of almotriptan in migraine can most likely be attributed to agonist effects at 5-HT$_{1B/1D}$ receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack, and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release, and reduced transmission in trigeminal pain pathways.

Pharmacokinetics

General: Almotriptan is well absorbed after oral administration (absolute bioavailability about 70%) with peak plasma levels 1 to 3 hours after administration; food does not affect pharmacokinetics. Almotriptan has a mean half-life of 3 to 4 hours. It is eliminated primarily by renal excretion (about 75% of the oral dose). Almotriptan is minimally protein bound (approximately 35%) and the mean apparent volume of distribution is approximately 180 to 200 liters.

Metabolism and Excretion: Almotriptan is metabolized by one minor and two major pathways. Monoamine oxidase (MAO)-mediated oxidative deamination (approximately 27% of the dose), and cytochrome P450-mediated oxidation (approximately 12% of the dose) are the major routes of metabolism, while flavin monooxygenase is the minor route. MAO-A is responsible for the formation of the indoleacetic acid metabolite, whereas cytochrome P450 (3A4 and 2D6) catalyzes the hydroxylation of the pyrrolidine ring to an intermediate that is further oxidized by aldehyde dehydrogenase to the gamma-aminobutyric acid derivative. Both metabolites are inactive.

Approximately 40% of an administered dose is excreted unchanged in urine. Renal clearance exceeds the glomerular filtration rate by approximately 3-fold, indicating an active mechanism. Approximately 13% of the administered dose is excreted via feces, both unchanged and metabolized.

Special Populations

Geriatric: Renal and total clearance, and amount of drug excreted in the urine were lower in elderly healthy volunteers (age 65 to 76 years) than in younger healthy volunteers (age 19 to 34 years), resulting in longer terminal half-life (3.7 h vs. 3.2 h) and a 25% higher area under the plasma concentration-time curve in the elderly subjects. The differences, however, do not appear to be clinically significant.

Pediatric: The pharmacokinetics of almotriptan in pediatric patients have not been evaluated.

Gender: No significant gender differences have been observed in pharmacokinetic parameters.

Race: No significant differences have been observed in pharmacokinetic parameters between Caucasian and African-American volunteers.

Hepatic impairment: The pharmacokinetics of almotriptan have not been assessed in this population. Based on the known mechanisms of clearance of almotriptan, the maximum decrease expected in almotriptan clearance due to hepatic impairment would be 60% (see DOSAGE AND ADMINISTRATION).

Renal impairment: The clearance of almotriptan was approximately 65% lower in patients with severe renal impairment (Cl/F=19.8 L/h; creatinine clearance between 10 and 30 mL/min) and approximately 40% lower in patients with moderate renal impairment (Cl/F=34.2 L/h; creatinine clearance between 31 and 71 mL/min) than in healthy volunteers (Cl/F= 57 L/h). Maximal plasma concentrations of almotriptan increased by approximately 80% in these patients (see DOSAGE AND ADMINISTRATION).

Drug Interactions (see also PRECAUTIONS, Drug Interactions)

All drug interaction studies were performed in healthy volunteers using a single 12.5-mg dose of almotriptan and multiple doses of the other drug.

Monoamine oxidase inhibitors: Coadministration of almotriptan and moclobemide (150 mg bid for 8 days) resulted in a 27% decrease in almotriptan clearance.

Propranolol: Coadministration of almotriptan and propranolol (80 mg bid for 7 days) resulted in no significant changes in the pharmacokinetics of almotriptan.

Selective serotonin reuptake inhibitors: Coadministration of almotriptan and fluoxetine (60 mg daily for 8 days), a potent inhibitor of CYP4502D6, had no effect on almotriptan clearance, but maximal concentrations of almotriptan were increased 18%. This difference is not clinically significant.

Verapamil: Coadministration of almotriptan and verapamil (120 mg sustained release tablets bid for 7 days), an inhibitor of CYP4503A4, resulted in a 20% increase in the area under the plasma concentration-time curve, and in a 24% increase in maximal plasma concentrations of almotriptan. Neither of these changes is clinically significant.

Ketoconazole and other potent CYP3A4 inhibitors: Coadministration of almotriptan and the potent CYP3A4 inhibitor ketoconazole (400 mg qd for 3 days) resulted in an approximately 60% increase in the area under the plasma concentration-time curve and maximal plasma concentrations of almotriptan. Although the interaction between almotriptan and other potent CYP3A4 inhibitors (eg, itraconazole, ritonavir, and erythromycin) has not been studied, increased exposures to almotriptan may be expected when almotriptan is used concomitantly with these medications.

CLINICAL STUDIES

The efficacy of AXERT Tablets was established in 3 multi-center, randomized, double-blind, placebo-controlled European trials. Patients enrolled in these studies were primarily female (86%) and Caucasian (more than 98%), with a mean age of 41 years (range of 18 to 72). Patients were instructed to treat a moderate to severe migraine headache. Two hours after taking one dose of study medication, patients evaluated their headache pain. If the pain had not decreased in severity to mild or to no pain, the patient was allowed to take an escape medication. If the pain had decreased to mild or to no pain at 2 hours but subsequently increased in severity between 2 and 24 hours, it was considered a relapse and the patient was instructed to take a second dose of study medication. Associated symptoms of nausea, vomiting, photophobia, and phonophobia were also evaluated.

In these studies, the percentage of patients achieving a response (mild or no pain) 2 hours after treatment was significantly greater in patients who received either AXERT 6.25 mg or 12.5 mg, compared with those who received placebo. A higher percentage of patients reported pain relief after treatment with the 12.5-mg dose than with the 6.25-mg dose. Doses greater than 12.5 mg did not lead to significantly better response. These results are summarized in Table 1.

Table 1. Response Rates 2 Hours Following Treatment of Initial Headache

	Placebo	AXERT 6.25 mg	AXERT 12.5 mg
Study 1	33.8% (N= 80)	55.4%* (N= 166)	58.5%† (N= 164)
Study 2	40.0% (N= 95)	---	57.1%‡ (N=175)
Study 3	33.0% (N= 176)	55.6%† (N= 360)	64.9%† (N= 370)

* p value 0.002 in comparison with placebo
† p value <0.001 in comparison with placebo
‡ p value 0.008 in comparison with placebo

These results cannot be validly compared with results of anti-migraine treatments in other studies. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria, under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment responses and the timing of response may be expected to vary considerably from study to study.

The estimated probability of achieving pain relief within 2 hours following initial treatment with AXERT is shown in Figure 1.

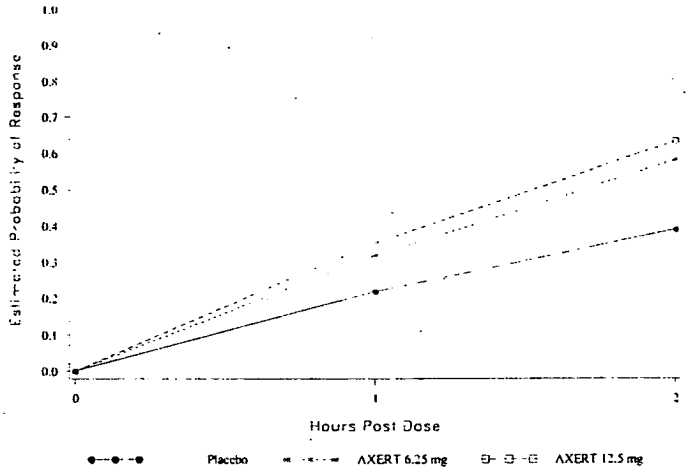


Figure 1. Estimated Probability of Achieving an Initial Headache Response (mild or no pain) in 2 Hours
This Kaplan-Meier plot is based on data obtained in the three placebo-controlled clinical trials that provided evidence of efficacy (Studies 1, 2, and 3). Patients not achieving pain relief by 2 hours were censored at 2 hours.

For patients with migraine-associated photophobia, phonophobia, nausea, and vomiting at baseline, there was a decreased incidence of these symptoms following administration of AXERT compared with placebo.

Two to 24 hours following the initial dose of study medication, patients were allowed to take an escape medication or a second dose of study medication for pain response. The estimated probability of patients taking escape medication or a second dose of study medication over the 24 hours following the initial dose of study medication is shown in Figure 2.

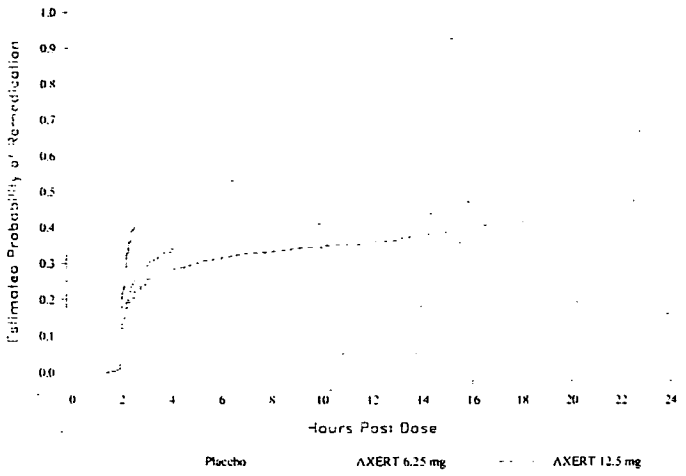


Figure 2. Estimated Probability of Patients Taking Escape Medication or a Second Dose of Study Medication Over the 24 Hours Following the Initial Dose of Study Treatment
This Kaplan-Meier plot is based on data obtained in the three placebo-controlled trials that provided evidence of efficacy (Studies 1, 2, and 3). Patients not using additional treatment were censored at 24 hours. Remedication was not allowed within 2 hours after the initial dose of AXERT.

The efficacy of AXERT was unaffected by the presence of aura; by gender, weight, or age of the patient; or by concomitant use of common migraine prophylactic drugs (eg, beta-blockers, calcium channel blockers, tricyclic antidepressants), or oral contraceptives. There were insufficient data to assess the effect of race on efficacy.

INDICATIONS AND USAGE

AXERT Tablets are indicated for the acute treatment of migraine with or without aura in adults.

AXERT is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of AXERT have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

AXERT Tablets should not be given to patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia), or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, or other significant underlying cardiovascular disease (see WARNINGS).

Because AXERT may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS).

AXERT should not be administered within 24 hours of treatment with another 5-HT_1 agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

AXERT should not be given to patients with hemiplegic or basilar migraine.

AXERT is contraindicated in patients who are hypersensitive to almotriptan or any of its ingredients.

WARNINGS

AXERT Tablets should only be used where a clear diagnosis of migraine has been established.

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: Because of the potential of this class of compounds (5-$HT_{1B/1D}$ agonists) to cause coronary vasospasm, AXERT should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that 5-HT_1 agonists (including AXERT) not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (eg, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular diseases or predisposition to coronary artery vasospasm is modest at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiogram (ECG), or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, AXERT should not be administered (see CONTRAINDICATIONS). For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of AXERT take place in the setting of a physician's office or similar medically staffed and equipped facility, unless the patient has previously received almotriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining an ECG during the interval immediately following the first use of AXERT in a patient with risk factors.

It is recommended that patients who are intermittent long-term users of AXERT and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use AXERT.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to AXERT.

Cardiac Events and Fatalities Associated with 5-HT_1 Agonists: Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low. Among the 3865 subjects/patients who received AXERT in premarketing clinical trials, one patient was hospitalized for observation after a scheduled ECG was found to be abnormal (negative T-waves on the left leads) 48 hours after taking a single 6.25-mg dose of almotriptan. The patient, a 48-year-old female, had previously taken 3 other doses for earlier migraine attacks. Myocardial enzymes at the time of the abnormal ECG were normal. The patient was diagnosed as having had myocardial ischemia, and it was also found that she had a family history of coronary disease. An ECG performed 2 days later was normal, as was a follow-up coronary angiography. The patient recovered without incident.

Cerebrovascular Events and Fatalities with 5-HT_1 Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with other 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (eg, stroke, hemorrhage, transient ischemic attack).

Other Vasospasm-Related Events: 5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT_1 agonists.

Increases in Blood Pressure: Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension treated with other 5-HT_1 agonists. AXERT is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). In volunteers, small increases in mean systolic and diastolic blood pressure relative to placebo were seen over the first 4 hours after administration of 12.5 mg of almotriptan (0.21 and 1.35 mm Hg, respectively). The effect of almotriptan on blood pressure was also assessed

in patients with hypertension controlled by medication. In this population, mean increases in systolic and diastolic blood pressure relative to placebo over the first 4 hours after administration of 12.5 mg of almotriptan were 4.87 and 0.26 mm Hg, respectively. The slight increases in blood pressure in both volunteers and controlled hypertensive patients were not considered clinically significant.

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT_1 agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

General: As with other 5-$HT_{1B/1D}$ agonists, sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw have been reported after treatment with AXERT Tablets. These events have not been associated with arrhythmias or ischemic ECG changes in clinical trials. Because drugs in this class may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT_1 agonist are candidates for further evaluation (see WARNINGS).

AXERT should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as those with impaired hepatic or renal function (see CLINICAL PHARMACOLOGY, Special Populations).

For a given attack, if a patient does not respond to the first dose of AXERT, the diagnosis of migraine headache should be reconsidered before the administration of a second dose.

Binding to Melanin-Containing Tissues: When pigmented rats were given a single oral dose of 5 mg/kg of radiolabeled almotriptan, the elimination half-life of radioactivity from the eye was 22 days. This finding suggests that almotriptan and/or its metabolites may bind to the melanin of the eye. Because almotriptan could accumulate in melanin-rich tissues over time, there is the possibility that it could cause toxicity in these tissues over extended use. However, no adverse retinal effects related to treatment with almotriptan were noted in a 52-week toxicity study in dogs given up to 12.5 mg/kg/day (resulting in systemic exposure [plasma AUC] to parent drug approximately 20 times that in humans receiving the maximum recommended daily dose of 25 mg). Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Corneal Opacities: Three male dogs (out of a total of 14 treated) in a 52-week toxicity study of oral almotriptan developed slight corneal opacities that were noted after 51, but not after 25, weeks of treatment. The doses at which this occurred were 2, 5, and 12.5 mg/kg/day. The opacity reversed in the affected dog at 12.5 mg/kg/day after a 4-week drug-free period. Systemic exposure (plasma AUC) to parent drug at 2 mg/kg/day was approximately 2.5 times the exposure in humans receiving the maximum recommended daily dose of 25 mg. A no-effect dose was not established.

Information for Patients: See PATIENT INFORMATION at the end of this labeling for the text of the separate leaflet provided for patients.

Laboratory Tests: No specific laboratory tests are recommended for monitoring patients.

Drug Interactions (see also CLINICAL PHARMACOLOGY, Drug Interactions)

Ergot-containing drugs: These drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and AXERT within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

Monoamine oxidase inhibitors: Coadministration of moclobemide resulted in a 27% decrease in almotriptan clearance and

an increase in C_{max} of approximately 6%. No dose adjustment is necessary.

Other 5-$HT_{1B/1D}$ agonists: Concomitant use of other 5-$HT_{1B/1D}$ agonists within 24 hours of treatment with AXERT is contraindicated (see CONTRAINDICATIONS).

Propranolol: The pharmacokinetics of almotriptan were not affected by coadministration of propranolol.

Selective serotonin reuptake inhibitors (SSRIs): SSRIs (eg, fluoxetine, fluvoxamine, paroxetine, sertraline) have been rarely reported to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT_1 agonists. If concomitant treatment with AXERT and an SSRI is clinically warranted, appropriate observation of the patient is advised.

Verapamil: Coadministration of almotriptan and verapamil resulted in a 24% increase in plasma concentrations of almotriptan. No dose adjustment is necessary.

Ketoconazole and other potent CYP3A4 inhibitors: Coadministration of almotriptan and the potent CYP3A4 inhibitor ketoconazole (400 mg qd for 3 days) resulted in an approximately 60% increase in the area under the plasma concentration-time curve and maximal plasma concentrations of almotriptan. Although the interaction between almotriptan and other potent CYP3A4 inhibitors (eg, itraconazole, ritonavir, and erythromycin) has not been studied, increased exposures to almotriptan may be expected when almotriptan is used concomitantly with these medications.

Drug/Laboratory Test Interactions: AXERT is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: The carcinogenic potential of almotriptan was evaluated by oral gavage for up to 103 weeks in mice at doses up to 250 mg/kg/day and in rats for up to 104 weeks at doses up to 75 mg/kg/day. These doses were associated with plasma exposures (AUC) to parent drug that were approximately 40 and 78 times, in mice and rats respectively, the plasma AUC observed in humans receiving the maximum recommended daily dose (MRDD) of 25 mg. Because of high mortality rates in both studies, which reached statistical significance in high dose female mice, all female rats, all male mice, and high dose female mice were terminated between weeks 96 and 98. There was no increase in tumors related to almotriptan administration.

Mutagenesis: Almotriptan was not mutagenic, with or without metabolic activation, in two *in vitro* gene mutation assays, the Ames test and the thymidine locus mouse lymphoma assay. Almotriptan was not clastogenic in an *in vivo* mouse micronucleus assay. Almotriptan produced an equivocal weakly positive response in *in vitro* cytogenetics assays in human lymphocytes.

Impairment of fertility: When female rats received almotriptan by oral gavage prior to and during mating and up to implantation at doses of 25, 100, and 400 mg/kg/day, prolongation of the estrous cycle was observed at a dose of 100 mg/kg/day (40 times the maximum recommended daily dose [MRDD] of 25 mg on a mg/m^2 basis). No effects on fertility were noted in female rats at 25 mg/kg/day (approximately 10 times the MRDD on a mg/m^2 basis).

Pregnancy: Pregnancy Category C: When almotriptan was administered by oral gavage to pregnant rats throughout the period of organogenesis at doses of 125, 250, 500, and 1000 mg/kg/day, an increase in embryolethality was seen at the highest dose (maternal exposure, based on plasma AUC of parent drug, was approximately 958 times the human exposure at the maximum recommended daily dose [MRDD] of 25 mg). Increased incidences of fetal skeletal variations (decreased ossification) were noted at doses greater than 125 mg/kg/day (maternal exposure 80 times human exposure at MRDD). Similar studies in rabbits conducted with almotriptan at doses of 5, 20, and 60 mg/kg/day demonstrated increases in embryolethality at the high dose (50 times the MRDD on a mg/m^2 basis). When almotriptan was administered to rats throughout the periods of gestation and lactation at doses of 25, 100, and 400 mg/kg/day, gestation length was increased and litter size and offspring body weight were decreased at the high dose (160 times the MRDD on a mg/m^2 basis).. The decrease in pup weight persisted throughout lactation. The no-observed-effect level in this study was 100 mg/kg/day (40 times the MRDD on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women; therefore AXERT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers: It is not known whether almotriptan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when AXERT is administered to a nursing woman. Lactating rats dosed with almotriptan had milk levels equivalent to maternal plasma levels at 0.5 hours and 7 times higher than plasma levels at 6 hours after dosing.

Pediatric use: Safety and effectiveness of AXERT in pediatric patients have not been established; therefore, AXERT is not recommended for use in patients under 18 years of age.

Postmarketing experience with other triptans include a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults. The long-term safety of almotriptan in pediatric patients has not been studied.

Geriatric Use: Clinical studies of AXERT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Clearance of almotriptan was lower in elderly volunteers than in younger individuals but there were no observed differences in the safety and tolerability between the two populations (see CLINICAL PHARMACOLOGY, Special Populations). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. The recommended dose of AXERT for elderly patients with normal renal function for their age is the same as that recommended for younger adults.

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following use of 5-HT$_1$ agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospams, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Incidence in Controlled Clinical Trials: Adverse events were assessed in controlled clinical trials that included 1840 patients who received one or two doses of AXERT Tablets and 386 patients who received placebo.

The most common adverse events during treatment with AXERT were nausea, somnolence, headache, paresthesia, and dry mouth. In long-term open-label studies where patients were allowed to treat multiple attacks for up to one year, 5% (63 out of 1347 patients) withdrew due to adverse experiences.

Table 2 lists the adverse events that occurred in at least 1% of the patients treated with AXERT, and at an incidence greater than in patients treated with placebo, regardless of drug relationship. These events reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Table 2. Incidence of Adverse Events in Controlled Clinical Trials (Reported in at Least 1% of Patients Treated with AXERT, and at an Incidence Greater than Placebo)

	Percent of Patients Reporting the Event		
Adverse Event	AXERT 6.25 mg (n=527)	AXERT 12.5 mg (n=1313)	Placebo (n=386)

Digestive			
Nausea	1	2	1
Dry Mouth	1	1	0.5
Nervous			
Paresthesia	1	1	0.5

AXERT is generally well tolerated. Most adverse events were mild in intensity and were transient, and did not lead to long-lasting effects. The incidence of adverse events in controlled clinical trials was not affected by gender, weight, age, presence of aura, or use of prophylactic medications or oral contraceptives. There were insufficient data to assess the effect of race on the incidence of adverse events.

Other Events: In this section, the frequencies of less commonly reported adverse events are presented. However, the role of AXERT in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used AXERT in controlled clinical trials and reported an event, divided by the total number of patients exposed to AXERT in these studies. All reported events are included, except the ones already listed in the previous table, those unlikely to be drug-related, and those poorly characterized. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; and rare adverse events are those occurring in fewer than 1/1000 patients.

Body: Frequent was headache. Infrequent were abdominal cramp or pain, asthenia, chills, back pain, chest pain, neck pain, fatigue, and rigid neck. Rare were fever and photosensitivity reaction.

Cardiovascular: Infrequent were vasodilation, palpitations, and tachycardia. Rare were hypertension, and syncope.

Digestive: Infrequent were diarrhea, vomiting, and dyspepsia. Rare were colitis, gastritis, gastroenteritis, esophageal reflux, increased thirst, and increased salivation.

Metabolic: Infrequent were hyperglycemia and increased serum creatine phosphokinase. Rare were increased gamma glutamyl transpeptidase and hypercholesteremia.

Musculoskeletal: Infrequent were myalgia and muscular weakness. Rare were arthralgia, arthritis, and myopathy.

Nervous: Frequent were dizziness and somnolence. Infrequent were tremor, vertigo, anxiety, hypesthesia, restlessness, CNS stimulation, insomnia, and shakiness. Rare were change in dreams, impaired concentration, abnormal coordination, depressive symptoms, euphoria, hyperreflexia, hypertonia, nervousness, neuropathy, nightmares, and nystagmus.

Respiratory: Infrequent were pharyngitis, rhinitis, dyspnea, laryngismus, sinusitis, bronchitis, and epistaxis. Rare were hyperventilation, laryngitis, and sneezing.

Skin: Infrequent were diaphoresis, dermatitis, erythema, pruritus, and rash.

Special Senses: Infrequent were ear pain, conjunctivitis, eye irritation, hyperacusis, and taste alteration. Rare were diplopia, dry eyes, eye pain, otitis media, parosmia, scotoma, and tinnitus.

Urogenital: Infrequent was dysmenorrhea.

DRUG ABUSE AND DEPENDENCE

Although the abuse potential of AXERT Tablets has not been specifically assessed, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received AXERT in clinical trials or their extensions. The 5-$HT_{1B/1D}$ agonists, as a class, have not been associated with drug abuse.

OVERDOSAGE

Patients and volunteers receiving single oral doses of 100 to 150 mg of almotriptan did not experience significant adverse events. Six additional normal volunteers received single oral doses of 200 mg without serious adverse events. During clinical trials with AXERT Tablets, one patient ingested 62.5 mg in a 5-hour period and another patient ingested 100 mg in a 38-hour period. Neither patient experienced adverse reactions.

Based on the pharmacology of 5-HT agonists, hypertension or other more serious cardiovascular symptoms could occur after overdosage. Gastrointestinal decontamination (ie, gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with AXERT. Clinical and electrocardiographic monitoring should be continued for at least 20 hours, even if clinical symptoms are not observed.

It is unknown what effect hemodialysis or peritoneal dialysis has on plasma concentrations of almotriptan.

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 6.25 mg and 12.5 mg of AXERT Tablets were effective for the acute treatment of migraines in adults, with the 12.5-mg dose tending to be a more effective dose (see CLINICAL STUDIES). Individuals may vary in response to doses of AXERT. The choice of dose should therefore be made on an individual basis.

If the headache returns, the dose may be repeated after 2 hours, but no more than two doses should be given within a 24-hour period. Controlled trials have not adequately established the effectiveness of a second dose if the initial dose is ineffective.

The safety of treating an average of more than four headaches in a 30-day period has not been established.

Hepatic impairment: The pharmacokinetics of almotriptan have not been assessed in this population. The maximum decrease expected in the clearance of almotriptan due to hepatic impairment is 60%. Therefore, the maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg should be used (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Renal impairment: In patients with severe renal impairment, the clearance of almotriptan was decreased. Therefore, the maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg should be used (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

HOW SUPPLIED

AXERT Tablets are available as follows:

6.25 mg: white, circular, biconvex tablet, printed in red with the code 2080.
Unit Dose (aluminum blister pack)
6 tablets NDC 0009-5141-02

12.5 mg: white, circular, biconvex tablet, printed in blue with a stylized A.
Unit Dose (aluminum blister pack)
6 tablets NDC 0009-4618-04

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Rx only

US Patent No. 5,565,447

Manufactured for: Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

By: Atlantic Pharmaceutical Services
Owings Mills, MD 21117, USA

Licensed from: Almirall Prodesfarma

[Date]
[Copy code]

PATIENT INFORMATION
The following wording is contained in a separate leaflet provided for patients.

Patient information about
AXERT™ Tablets
Generic name: almotriptan malate tablets

Please read this information before you start taking AXERT Tablets. Also, read this leaflet each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss AXERT when you start taking your medication and at regular checkups.

What is AXERT and what is it used for?
AXERT is a medication used to treat migraine attacks in adults. AXERT is a member of a class of drugs called selective serotonin receptor agonists.

Use AXERT only for a migraine attack. Do not use AXERT to treat headaches that might be caused by other conditions. Tell your doctor about your symptoms. Your doctor will decide if you have migraine.

There is more information about migraine at the end of this leaflet.

Who should not take AXERT? *
Do not take AXERT if you:

- have ever had heart disease.
- have uncontrolled high blood pressure.
- have hemiplegic or basilar migraine. If you are not sure, ask your doctor.
- have taken another serotonin receptor agonist in the last 24 hours. These include naratriptan (AMERGE™), rizatriptan (MAXALT®), sumatriptan (IMITREX®), or zolmitriptan (ZOMIG™).
- have taken ergotamine-type medicines in the last 24 hours. These include ergotamine (BELLERGAL-S®, CAFERGOT®, ERGOMAR®, WIGRAINE®), dihydro-ergotamine (D.H.E. 45®), or methysergide (SANSERT®).
- had an allergic reaction to AXERT or any of its ingredients. The active ingredient is almotriptan malate. As your doctor or pharmacist about inactive ingredients.

Tell your doctor if you take

- monoamine oxidase (MAO) inhibitors, such as phenelzine sulfate (NARDIL®) or tranylcypromine sulfate (PARNATE®) for depression or another condition, or if it has been less than two weeks since you stopped taking a MAO inhibitor.
- ketoconazole (NIZORAL®), itraconazole (SPORANOX®), ritonavir (NORVIR®), or erythromycin (EMYCIN®), or if it has been less than one week since you stopped taking one of these drugs.

These medicines may affect how AXERT works, or AXERT may affect how these medicines work.

To help your doctor decide if AXERT is right for your or if you need to be checked while taking AXERT, tell your doctor about any

- past or present medical problems
- past or present high blood pressure, chest pain, shortness of breath, or heart disease
- liver or kidney problems
- risk factors for heart disease, such as:
  - high blood pressure
  - diabetes
  - high cholesterol

* The brands listed are the trademarks of their respective owners and are not trademarks of Pharmacia & Upjohn, Inc.

  - overweight
  - smoking
  - family members with heart disease
  - You are past menopause
  - You are a male over 40 years old
- plans to become pregnant, or if you are pregnant, might be pregnant, or do not use effective birth control
- plans to breast-feed, or if you are already breast-feeding
- medicines you are take or plan to take, including prescription and non-prescription medicines and herbal supplements. Be sure to include medicines you normally take for a migraine.

How should I take AXERT?

- When you have a migraine headache, take your medicine as directed by your doctor.
- If your headache comes back after your first dose, you may take a second dose 2 hours or more after the first dose. If your pain continues after the first dose, do not take a second dose without first checking with your doctor.
- Do not take more than two AXERT tablets in a 24-hour period.
- If you take too much medicine, contact your doctor, hospital emergency department, or poison control center right away.

What should I avoid while taking AXERT?

Check with your doctor before you take any new medicines, including prescription and non-prescription medicines and supplements. There are some medicines that you should not take during the period 24 hours before and 24 hours after taking AXERT. Some of them are listed in the section "Who should not take AXERT?"

What are the possible side effects of AXERT?

AXERT is generally well tolerated. The side effects are usually mild and do not last long. The following is **not** a complete list of side effects. Ask your doctor to tell you about the other side effects.

The **most common** side effects are

- Nausea
- Sleepiness
- Tingling or burning feeling (paresthesia)
- Headache
- Dry mouth

If you experience sleepiness, you should evaluate your ability to perform complex tasks such as driving or operating heavy machinery.

Tell your doctor about any other symptoms that you develop while taking AXERT. If the symptoms continue or worsen, get medical help right away. Also, tell your doctor if you develop a rash or itching after taking AXERT. You may be allergic to the medicine.

In very rare cases, patients taking this class of medicines experience serious heart problems, stroke, or increased blood pressure. Extremely rarely, patients have died. Therefore, tell your doctor right away if you feel tightness, pain, pressure or heaviness in your chest, throat, neck, or jaw after taking AXERT. Do not take AXERT again until your doctor has checked you.

What is migraine and how does it differ from other headaches?

Migraine is an intense, throbbing, typically one-sided headache. It often includes nausea, vomiting, sensitivity to light, and sensitivity to sound. The pain and symptoms from a migraine headache may be worse than the pain and symptoms of a common headache.

Some people have visual symptoms before the headache, such as flashing lights or wavy lines, called an aura.

Migraine attacks typically last for hours or, rarely, for more than a day. They can return often. The strength and frequency of migraine attacks may vary.

Based on your symptoms, your doctor will decide whether you have migraine.

Migraine headaches tend to occur in members of the same family. Both men and women get migraine, but it is more common in women.

What may trigger a migraine attack?
Certain things may trigger migraine attacks in some people. Some of these triggers are:

- Certain foods or drinks, such as cheese, chocolate, citrus fruit (oranges, grapefruit, lemons, lime, and others), caffeine, and alcohol
- Stress
- Change in behavior, such as too much or too little sleep, missing a meal, or a change in diet
- Hormone changes in women, such as during monthly menstrual periods

You may be able to prevent migraine attacks or make them come less often if you understand what triggers your attacks. Keeping a headache diary may help you identify and monitor the possible triggers that cause your migraine. Once you identify the triggers, you and your doctor can change your lifestyle to avoid those triggers.

How does AXERT work during a migraine attack?
Treatment with AXERT:

- Reduces swelling of blood vessels surrounding the brain. This swelling is associated with the headache pain of a migraine attack.
- Blocks the release of substances from nerve endings that cause more pain and other symptoms of migraine.
- Interrupts the sending of specific pain signals to your brain.

It is thought that each of these actions contributes to relief of your symptoms by AXERT.

How should I store AXERT?
Keep your medicine in a safe place where children cannot reach it. It may be harmful to children. Store your medicine away from heat, light, or moisture, at a controlled room temperature. If your medicine has expired, throw it away as instructed. If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to do so. Throw away your medicine as instructed. Be sure that discarded tablets are out of the reach of children.

General advice about prescription medicines
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use AXERT for a condition for which it was not prescribed. Do not give AXERT to other people, even if they have the same symptoms you have. People may be harmed if they take medicines that have not been prescribed to them.

This leaflet provides a summary of information about AXERT. If you have any questions or concerns about either AXERT or migraines, talk to your doctor. In addition, talk to your pharmacist or other health care provider.

US005565447A

United States Patent [19]

Forner et al.

[11] Patent Number: 5,565,447

[45] Date of Patent: Oct. 15, 1996

[54] **INDOLE DERIVATIVES**

[75] Inventors: **Dolors F. Forner; Carles P. Duran; Jose P. Soto; Armando V. Noverola; Jacinto M. Mauri**, all of Barcelona, Spain

[73] Assignee: **Laboratorios Almirall S.A.**, Spain

[21] Appl. No.: **437,682**

[22] Filed: **May 9, 1995**

Related U.S. Application Data

[63] Continuation of Ser. No. 211,446, Mar. 28, 1994, abandoned.

[30] **Foreign Application Priority Data**

Jul. 28, 1992 [GB] United Kingdom 9216009

[51] **Int. Cl.**[6] **A61K 31/445**; A61K 31/495; C07D 401/12; C07D 403/12

[52] **U.S. Cl.** **514/212**; 514/253; 514/323; 514/414; 514/235.2; 540/602; 544/143; 544/373; 546/201; 548/467

[58] **Field of Search** 548/467; 544/373; 546/201; 540/602; 514/212, 253, 323, 414

[56] **References Cited**

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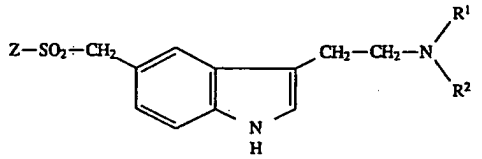
Primary Examiner—Emily Bernhardt
Attorney, Agent, or Firm—Spencer & Frank

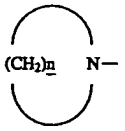
[57] **ABSTRACT**

A compound of formula (I)



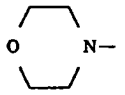
(I)

wherein R^1 and R^2 each represents a hydrogen atom or an alkyl group, Z represents a ring selected from:

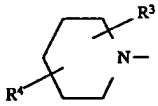


II

in which n represents 4, 5 or 6;

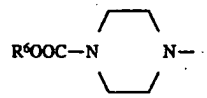


III



IV

in which R^3 represents hydrogen or an alkyl group and R^4 represents an alkyl, methoxy benzyl or R^5 NHCO group, R^5 being an alkyl group; and



V

in which R^6 represents an alkyl group.

and pharmaceutically acceptable salts thereof are useful in the treatment of migraine and other conditions. They are prepares by decarboxylation of the corresponding indolyl 2-carboxylic acid.

6 Claims, No Drawings

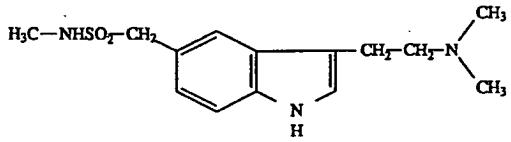
INDOLE DERIVATIVES

This application is a continuation of application Ser. No. 08/211,446, filed Mar. 28, 1994, now abandoned which application is a 371 of PCT/EP93/01901 filed Jul. 19, 1993.

THIS INVENTION relates to new indol derivatives, methods for their preparation, compositions containing them and their use in medical treatment.

The mechanism involved in the genesis of a migraine attack is not known, but it has been demonstrated that the large intracranial vessels are distended during the headache phase. Some compounds like ergotamine and serotonine (5-Hydroxytryptamine; 5-HT), have a vasoconstrictor action in the carotid vascular bed by an agonistic action at the "5-HT_1-like" receptors. However, the lack of selectivity of these compounds is the cause of undesirable and potentially dangerous side-effects.

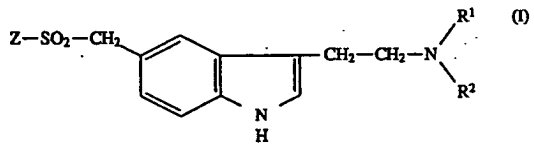
In British Patents 2124210A and 2162532A, new anti-migraine compounds have been disclosed and seem to stimulate more selectively a sub-population of "5-HT_1-like" receptors. Among these compounds, Sumatriptan of formula:



is available for migraine therapy. This compound presents a high affinity for 5-HT_{1D} receptor but it has also a very important affinity for 5-HT_{1A} receptor. This affinity for 5-HT_{1A} receptor, causes hypotension by a central nervous system action and other side effects.

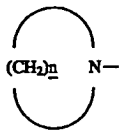
We have now found that the introduction of a nitrogen ring in the methanesulfonyl group provides new anti-migraine compounds that present a greater affinity for 5-HT_{1D} receptor than for 5-HT_{1A} receptor and therefore, less side-effects.

Accordingly, the present invention provides a compound of formula:



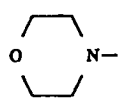
(I)

wherein R^1 and R^2 each represent a hydrogen atom or an alkyl group, Z represents a ring selected from:

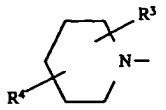


II

in which nrepresents 4, 5 or 6;

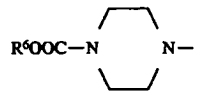


III



IV

in which R^3 represents hydrogen or an alkyl group R^4 represents an alkyl, methoxy, benzyl or R^5 NHCO group, R^5 being an alkyl group; and



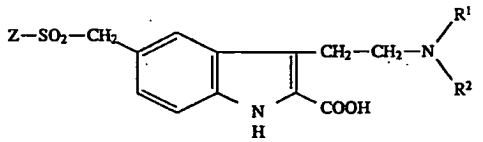
V

in which R^6 represents an alkyl group;
and pharmaceutically acceptable salts thereof.

The alkyl group mentioned in relation with the groups R^1, R^2, R^3, R^4, R^5 and R^6 in compounds of the invention, are usually "lower" alkyl, that is containing up to 6 and particularly up to 4 carbon atoms, the hydrocarbon chain being branched or straight.

The compounds of general formula I wherein R^1 and R^2 are alkyl groups and Z is II or V are preferred.

According to a feature of the present invention the indol derivatives of general formula I may be prepared by the process which comprises a decarboxylation of a carboxylic acid of general formula VI:



(VI)

(wherein the various symbols are as defined above). The reaction is preferably carried out in an inert organic solvent as quinoline, tri-n-butylamine, N,N-dimethylacetamide or pyridine, in the presence of a catalyst as copper powder, cupric oxide, cuprous oxide or other copper derivatives, at a temperature between 100° and 200° C.

The intermediates VI used in the preparation of the compounds of the invention, were prepared by known processes described in the literature (A. Gonzalez, Synth. Commun. (1991)), 21, 669; B. A. Howell, J. Chem. Ed. 176 (1984); H. Plieninger, Ber. (1950), 83, 268).

Indol derivatives of general formula I can be converted by methods known per se into acid addition salts with acids in appropriate solvents, for example acetone, alcohols, dioxane or tetrahydrofuran. Suitable acid addition salts are those derived from inorganic acids, for example the hydrochlorides and sulphates.

The experiments with usual test animals were conducted and evaluated in the following manner:

Dog Saphenous Vein

Isometric recordings were performed essentially as described by Humphrey et al (1988). Briefly, lateral saphenous vein ring preparations (3 mm. wide) removed from anaesthetized beagle dogs were suspended under 2g. resting tension, in 30 mL organ baths containing Krebs at 37° C. The experiments were carried out in the presence of 5-HT2, H1 and muscarinic antagonists and serotonin 1 μM was used as quantitative reference standard.

(Humphrey P. P. A.; Feniuk W.; Perren M. J.; Connor H. E.; Oxford A. W .; Coates I. H. and Butina D. (1988). GR 43175, a selective agonist for the 5-HT1-like receptor in dog isolated saphenous vein. Br. J. Pharmac. 94, 1123–1132).

Binding to 5HT1D Receptors

Assays were performed essentially as described by Bruinvels et al. Varying amounts of tested drugs were added to

0.25 mL final volume reaction that included 100 μg of calf caudate nucleus membrane protein, 100 pM (Serotonin-5-0-Carboxymethyl-Glycyl[^{125}I]Tyrosinamide (^{125}I-GTI), 4 mM $CaCl_2$ and 50 mM Tris HCl buffer, pH 7.4. After incubation at 37° C. for 30 minutes, samples were filtered under reduced pressure using glass fibre filters. The filters were washed with ice-cold buffer and dried. Non-specific binding was defined as that obtained in the presence of 10 μM 5HT. Trapped radioactivity was quantified using a gamma counter. Displacement curves were constructed and the concentration displacing 50% of radioligand was calculated for each tested compound using non-linear regression. Data from at least three different assays run in duplicate was averaged. (Bruinvels A. T.; Lery H.; Palacios J. M. and Hoyer D. 5-HT_{1D} binding sites in various species: similar pharmacological profile in dog, monkey, calf, guinea-pig and human brain membranes. Naunyn-Schmiedeberg's Arch. Pharmacol. (in press)).

Binding to 5HT1A receptors

Assays were performed essentially as described by Gozlan et al (1983). Varying amounts of tested drugs were added to 1 mL final volume reaction mixtures that included 100 μg of rat hippocampus membrane protein, 0.5 nM ^{3}H-8-OH-DPAT, 4 mM $CaCl_2$, 0.1% ascorbic acid, 10 μM pargyline and 50 mM Tris HCl buffer, pH 7.4. After incubation at 25° C. for 30 minutes, samples were filtered under reduced pressure using glass fibre filters. The filters were washed with ice-cold buffer and dried. Non-specific binding was defined as that obtained in the presence of 10 μM 5HT. Radioactivity was quantified by scintillation counting and data was handled as described for the 5HT_{1D} binding assay. (Gozlan H.; El Mestikawy S.; Pichat L.; Glowinski J. and Hamon M. (1983). Identification of presynaptic serotonin autoreceptors using a new ligand:^{3}H-PAT. Nature 305, 140–142).

The results of the tests described above, using compounds according to the invention (see Examples below) and, as a comparison, Sumatriptan, are shown in Table I below:

TABLE I

	Results of different pharmacological test			
	Dog saphenous vein pD2	Binding IC50 nM 125I-GTI	3H-8-OH-DPAT	5HT1A/5HT1D
Sumatriptan	6.06 ± 0.01	10.4 ± 1	460 ± 67	44.2
1	6.06 ± 0.03	10.7 ± 0.4	825 ± 69	77.1
2	5.92 ± 0.10	6.9 ± 0.4	340 ± 0.5	49.3
11	6.47 ± 0.03	3.2 ± 0.3	850 ± 40	265.6

From results presented above it can be concluded that the novel compounds of this invention demonstrate binding selectivity for 5-HT1D receptors and vasoconstrictor capability mediated by an agonism on 5HT1D receptors. According to the results this invention provides compounds with potential interest for the treatment or prevention of migraine and other headache associated with vascular disorders (e.g. cluster headache and chronic paroxysmal hemicrania), with administration of substances or their withdrawal, and for the treatment or prevention of tensional cephaliar pain, movement disorders, depression and anxiety.

Thus, the present invention provides indol derivatives of the formula I and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such derivatives and salts thereof, for use in the treatment or therapy of the human body.

Accordingly, the indol derivatives of the formula I and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such derivatives and salts thereof, may be used in a method of treatment of disorders of the human body which comprises administering to a recipient in need of such therapy an effective amount of said derivatives or salts thereof or said compositions.

The present invention also provides pharmaceutical compositions which comprise, as active ingredient, at least one compound of general formula I, or a pharmacologically acceptable salt in association with a pharmaceutically acceptable carrier or diluent. The active ingredient may comprise 0.001% to 99% by weight, preferably 0.01% to 90% by weight of the composition depending upon the nature of the formulation and whether further dilution is to be made prior to application. Preferably the compositions are made up in a form suitable for oral, topical, percutaneous or parenteral administration.

The pharmaceutically acceptable carriers or diluents which are admixed with the active compound, or compounds or salts of such compounds, to form the compositions of this invention are well-known per se and the actual excipients used depend inter alia on the intended method of administering the compositions. Compositions of this invention are preferably adapted for administration parenteral and per os. In this case, the composition for oral administration may take the form of tablets, capsules or liquid preparations, such as mixtures, elixirs, syrups or suspensions, all containing one or more compounds of the invention; such preparations may be made by methods well-known in the art.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents, if desired. Tablets or capsules may conveniently contain between 1 and 200 mg of active ingredient or the equivalent amount of a salt thereof.

The liquid composition adapted for oral use may be in the form of solutions or suspensions. The solutions may be aqueous solutions of a soluble salt or other derivative of the active compound in association with, for example, sucrose to form a syrup. The suspensions may comprise an insoluble active compound of the invention or a pharmaceutically acceptable salt thereof in association with water, together with a suspending agent or flavouring agent.

Compositions for parenteral injection may be prepared from soluble salts, which may or may not be freeze-dried and which may be dissolved in water or an appropriate parenteral injection fluid.

Effective doses are normally in the range of 10–600 mg of active ingredient per day.

The following Examples illustrate the preparation of compounds of the present invention.

EXAMPLE 1

To a solution of previously dried 1-[[2-carboxy-3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]pyrrolidine (1.6 g; 0.0442 moles) in anhydrous quinoline (75 ml) and under atmosphere of nitrogen, cuprous oxide (160 mg; 0.0011 moles) was added. The reaction mixture was heated to 190° C. for 15 minutes, stirred to room temperature, poured into a mixture of 1N hydrochloric acid (150 ml) and ethyl acetate (50 ml), shaken and decanted. The aqueous solution was washed several times with ethyl acetate, then solid sodium bicarbonate was added until pH=7.8, and washed with n-hexane to eliminate the quinoline. The aqueous solution was made alkaline with solid potassium car-

bonate and extracted with ethyl acetate. The organic solution was dried (Na_2SO_4), the solvent removed under reduced pressure when a dark oil was obtained (1.3 g; yield 92%). This product was purified by column chromatography with silica gel and methylene chloride:ethanol:ammonium hydroxide (60:8:1) as eluent and a white foam (0.8 g) of 1-[[3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl] pyrrolidine was obtained.

To a solution of the above product (0.8 g) in acetone (30 ml), a few drops of hydrogen chloride saturated dioxan solution, were added. The precipitated solid was collected by filtration, washed with acetone and dried to give 1-[[3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]-pyrrolidine hydrochloride (0.75 g). Melting point 218°–220° C.

Further indol derivatives of general formula I as set out in Table 2 below were prepared according to the process disclosed in Example 1 but using the appropriately substituted reactants VI.

TABLE 2

COMPOUND No.	R^1; R^2	Z	DERIVATIVE	M.P °C.
1	$R^1 = R^2 = CH_3$	II; n = 4	HCl	218–220
2	$R^1 = R^2 = CH_3$	II; n = 5	HCl	225–227(d)
3	$R^1 = R^2 = CH_3$	II; n = 6	hydrogen succinate	127–130(d)
4	$R^1 = H$; $R^2 = CH_3$	II; n = 4	HCl	177–178
5	$R^1 = R^2 = CH_3$	III	HCl	231–232(d)
6	$R^1 = R^2 = CH_3$	IV; $R^3 = H$; $R^4 = 4\text{-}CH_3$	hydrogen succinate	151–153
7	$R^1 = R^2 = CH_3$	IV; $R^3 = R^4 = 4\text{-}CH_3$	hydrogen succinate	170–172
8	$R^1 = R^2 = CH_3$	IV; $R^3 = H$; R^4 = methoxy	hydrogen succinate	143–145
9	$R^1 = R^2 = CH_3$	IV; $R^3 = H$; R^4 = benzyl	HCl	225–227
10	$R^1 = R^2 = CH_3$	IV; $R^3 = H$; $R^4 = H_3CNHCO$	base	161–163
11	$R^1 = R^2 = CH_3$	V; $R^6 = C_2H_5$	base	170–171

EXAMPLE 2

20,000 Ampoules each containing 10 mg. of 1-[[3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]piperidine hydrochloride (active ingredient) were prepared from the following formulation:

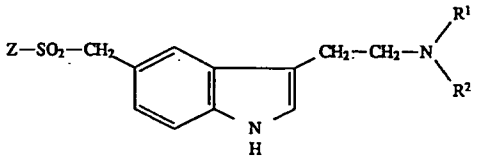
Active ingredient	200 g
Sodium chloride	200 g
Water injectable grade q.s.	40 liters

Procedure

The active ingredient and sodium chloride were dissolved in 40 litres of water, then passed through a bacteria-retaining filter and filled under sterile conditions into 2 ml glass ampoules in known manner.

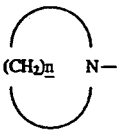
We claim:

1. A compound of formula (I)



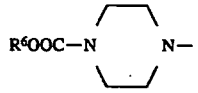
(I)

wherein R^1 and R^2 each represents a hydrogen atom or a C_{1-6} alkyl group, Z represents a ring selected from:



II

in which n represents 4, 5 or 6;



V

in which R6 represents a C_{1-6} alkyl group,

or pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 in which R^1 and R^2 which by the same or different is each C_{1-4} alkyl, and Z is of the formula II.

3. 1-[[3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]pyrrolidine;

1-[[3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]piperidine; or

1-[[3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]-4-ethoxycarbonyl piperazine; or a hydrochloride salt thereof.

4. A composition comprising a compound according to claim 1 mixed with a pharmaceutically acceptable carrier or diluent.

5. A method of treating headaches, movement disorders, depression or anxiety which comprises administering to a human or animal subject in need of treatment of an effective amount of a compound according to claim 1.

6. A method according to claim 5 wherein said treatment is for a migraine.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,565,447

DATED : Oct. 15, 1996

INVENTOR(S) : Dolors F. Forner, et al

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 1:

Line 62, DELETE "nrepresents" INSERT, therefor:

--n represents--

Column 6: Line 34, DELETE "which by the same" INSERT, therefor:

--which are the same--.

Signed and Sealed this

Ninth Day of September, 1997

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

5

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,565,447

DATED : October 15, 1996

INVENTOR(S) : Dolors F. Forner; Carles P. Duran; Jose P. Soto; Armando V. Noverola; Jacinto M. Mauri

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Title page:

Item 63: DELETE "Continuation of Ser. No. 211,446, Mar. 28, 1994, abandoned" INSERT, therefor:

--Continuation of Ser. No. 211,446, **filed Mar. 28,** 1994, abandoned, which is a 371 of PCT/EP93/01901, **filed July 19, 1993.**—

Signed and Sealed this

Eleventh Day of March, 1997

Bruce Lehman

BRUCE LEHMAN

Commissioner of Patents and Trademarks

Attest:

Attesting Officer

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

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WASHINGTON DC 20005-3955

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.
If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(h).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,565,447	183	830	----	08/437,682	10/15/96	05/09/95	04	NO	PAID

ITM NBR	ATTY DKT NUMBER
1	KEMPJ0016

**DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, D.C. 20231**

Table 5. Summary of FDA/Pharmacia & Upjohn Interactions Regarding the Almotriptan Clinical Development Program

Interaction	Date	Summary
Change of IND Ownership (Amendment Serial Nos. 007 and 008)	25 March 1998	Ownership of IND 53,854 transferred from Almirall Prodesfarma, S.A. (APF) to Pharmacia & Upjohn (P&U).
Amendment Serial No. 011	16 April 1998	Pre-NDA Briefing Document was submitted that presented the general preclinical and clinical information to be included in the NDA and outlined issues for discussion at a future pre-NDA meeting. CMC issues were to be discussed at a separate meeting.
Telecon-ference	21 April 1998	NDA number assigned 21-001; expected filing December 1998
Amendment Serial No. 014	28 May 1998	Requested a pre-NDA meeting to discuss CMC portion of NDA. Also requested FDA concurrence that the consolidation of the tablet manufacturing and compressing/coating operations onto one campus would not be considered a site change requiring the generation of additional stability lots prior to NDA submission. FDA concurrence was also requested on a plan to manufacture for market introduction at either the 200,000 or 1,200,000 scale at Atlantic Pharmaceutical Services, Inc. in Owings Mills, MD. A teleconference was requested.
Telefax to FDA	10 June 1998	Revised portions of the Pre-NDA Briefing Document—proposed submitting CRTs only as SAS data sets in transport format in lieu of domain and patient profiles, in accordance with FDA's Draft Guideline (Federal Register 18 April 1998). CRFs are to be submitted electronically in accordance with FDA's (September 1997) Guidance to Industry, "Archiving Submissions in Electronic Format – NDAs."
Telefax from FDA	16 June 1998	Response from Lana Chen (Project Manager) regarding CMC questions posed in Serial No. 014. The Agency considers consolidation of two existing manufacturing sites to be a level 3 site change (non-contiguous campus) and referenced a draft stability guidance which issued 15 June 1998. The Agency had no problem with the manufacture of 200,000 or 1,200,000 tablet lots for market introduction assuming the 200,000 tablet batch to be a pilot scale, since this falls within the scope of the SUPAC-IR.
Letter	16 June 1998	From Paul Leber (FDA) to Mark Baumgartner (P&U) confirming a 29 August 1997 communication to Dr. Barbara Loughman, Pharmaceutical Research Associates, Inc. (PRA) – authorized U.S. representative for APF – that stated the FDA had no objection to the initiation of proposed clinical studies pursuant to IND 53,854. Preclinical Issues: Additional pharmacology/toxicology information was requested. Specifically, critical toxicology studies were requested to be repeated with drug batches containing methyltryptamine levels comparable to those in the clinical batches; and it was recommended that the validity of in vitro genetic toxicology tests be ensured by demonstrating that all

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Table 5. Summary of FDA/Pharmacia & Upjohn Interactions Regarding the Almotriptan Clinical Development Program

Interaction	Date	Summary
		human metabolites are formed by the S9 activation system. It was noted that either the in vitro chromosomal aberration assay or the mouse lymphoma/thymidine kinase assay would fulfill current genotoxicity testing requirements. Clinical Issues: The FDA requested that P&U instruct patients to record the time of remedication; that P&U consider randomizing the second dose to gain information on the efficacy of a second dose; that the long-term safety database conform to ICH guidelines for exposures of at least 300 patients treating a minimum of 2 headaches per month for 6 months, and 100 patients treating a minimum of 2 headaches per month for 1 year; submission of a detailed review of ECG findings known to date concerning QTc intervals in animals and humans, collected shortly after drug administration; and evaluation of doses lower than 12.5 mg.
Telecon-ference	17 June 1998	Lana Chen confirmed that preclinical issues in the letter of 16 June and two of the clinical issues had not been previously communicated to either APF or to P&U. She suggested that P&U be prepared to discuss preclinical issues at the Pre-NDA meeting on 23 June.
Pre-NDA Meeting (Summary in Serial No. 019 27 July 1998)	23 June 1998	Pre-NDA meeting to discuss preclinical and clinical issues. FDA clarified criteria for collection of long-term safety data. Agreement that submission of non-US data would be acceptable if it meets requirements of 21 CFR 314.106. FDA stated mouse and rat carcinogenicity studies were required to continue through 104 weeks, typically with a minimum of 20 animals per group; the reviewers wished to be consulted prior to any action to end the study early due to survival issues. FDA confirmed that the methyltryptamine impurity issue had been adequately addressed, avoiding the necessity of repeating the preclinical studies as described in FDA's letter of 16 June 1998. Dr. Steele commented that the NDA needs to include details on impurities in drug lots used in clinical and preclinical supplies. FDA stated P&U must investigate the possibility of QTc prolongation in humans based on FDA concerns from preclinical data. FDA suggested P&U compare language in proposed labeling against that for recently approved drugs in the same class, as FDA intends to maintain labeling consistency.
Amendment Serial No. 018	20 July 1998	Requesting FDA agreement with proposed criteria for early termination of rat studies due to excess mortality in female groups.
Telecon-ference	24 July 1998	Mark Baumgartner (P&U) reiterated our desire for FDA response to proposal for early euthanasia in the carcinogenicity studies. Informed FDA of change in filing plan to file sometime in 1999 rather than in December 1998.
Telecon-ference	30 July 1998	Held with Pharmacology reviewers to discuss activities related to the excess mortality observed in the female groups in the 104-week rat carcinogenicity study. In addition, discussed the general plans should a similar situation be encountered in the ongoing mouse carcinogenicity study.
Amendment Serial No. 020	7 August 1998	Pre- NDA meeting Briefing Document concerning CMC issues for discussion. (A correction to page 8 of the Briefing Document was submitted in Amendment Serial No. 021, dated 18 August 1998.)

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Table 5. Summary of FDA/Pharmacia & Upjohn Interactions Regarding the Almotriptan Clinical Development Program

Interaction	Date	Summary
Pre-NDA meeting (Summary in Serial No. 023 2 Sept. 1998)	25 August 1998	Pre-NDA meeting focusing on CMC issues. Dr. Baweja commented that the combination of bioequivalence data and dissolution profile would provide a strong package. Discussed FDA preferred assay methods and identification testing methods. FDA confirmed that data from one lot of 12.5-mg tablets with 6-month accelerated comparative stability data would be sufficient to support site consolidation from Pharmaceutical Technology Center to Atlantic Pharmaceutical Services. FDA agreed that additional stability data for the 6.25-mg tablets submitted 6 months after filing would not be considered a major amendment. FDA noted that a rationale must be provided for not studying drug in patients with hepatic impairment.
Telecon-ference	21 January 1999	Roberta Krieger (P&U) suggested possibility of early submission of Item 5 (Pharmacology/Toxicology) and Item 6 (Pharmacokinetics). Lana Chen to check with reviewers on the acceptability of a rolling submission.
Correspon-dence Serial No. 037	25 February 1999	Requested opinion from Labeling and Nomenclature Committee on a proposed trademark—AXERT. NDA 20-001 for almotriptan tablets scheduled for submission December 1999.
Correspon-dence Serial No. 041	22 April 1999	Proposal for NDA 21-001. Item 2: requested evaluation and comments on draft package insert. Items 8 and 10: requested agreement on format of Clinical Data section and Statistical section—plan to submit Item 10 as an exact copy of Item 8. Item 11, CRTs: Proposed to submit all collected and derived data for all Phase 2 and III protocols not as patient profiles, but only as domain data sets in SAS transport format. Item 12, CRFs: Proposed to submit CRFs as pdf files for any patient who died or who dropped out of the study due to adverse events, across all studies (in accordance with FDA's September 1997 Guidance to Industry, "Archiving Submissions in Electronic Format – NDAs"). Item 19, Financial Disclosure: Listed studies P&U considers to be "covered" under Final Rule "Financial Disclosure by Clinical Investigators (Federal Register 2 February 1998).
Tele-conference	17 May 1999	Regarding our proposal for NDA submission, Lana Chen confirmed that patterning the format and content of the package insert after that of approved triptans was the right thing to do. Chen recommended that P&U submit proposal to FDA regarding conduct of pediatric studies or waiver. Chen confirmed that our plan to submit Item 10 as an exact copy of Item 8 was acceptable. Also, our plan on submitting Items 11 and 12 electronically was fine, as the statisticians normally just work with SAS transport files. Chen confirmed that the Nomenclature Committee had no objection to proposed trademark, AXERT.
Correspon-dence Serial No. 044	23 July 1999	At Lana Chen's recommendation, a letter was sent to Linda Carter (FDA) requesting confirmation that our plan for submission of financial information is appropriate and would meet requirements outlined in 63 FR 5233.
Correspon-dence Serial No. 049	7 October 1999	Request for Pediatric Waiver

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Author: Marcia J Rogers at PN04PO
Date: 5/22/01 2:04 PM
Normal
TO: Bruce A Pokras at USCHQPO4
Subject: AXERT NDA 21-001 submission log
---------- Message Contents

Bruce,

As requested, attached is the submission log of interactions with the FDA for AXERT Tablets (almotriptan tablets).

Below, I've compiled a brief list of some of the major milestones:

20 December 1999	NDA submitted
16 October 2000	3-month extension of the primary user fee date due to P&U submission of reports for FDA-requested repeated tox studies
13 December 2000	P&U presentation at Full Carcinogenicity Assessment Committee meeting resolved Tox issue
20 December 2000	Approvable Letter issued
23 January 2001	"Complete Response" submitted
5 February 2001	Additional questions from CMC Reviewer (clarified in 14 February 2001 teleconference)
6 March 2001	CMC Submission to complete the Complete Response
7 May 2001	FDA Approval
7 May 2001	letter from P&U to transfer NDA 21-001 ownership to G.D. Searle LLC
8 May 2001	letter from G.D. Searle LLC accepting ownership of NDA 21-001

Hope this is helpful to you.

Marcia

NDA NO. 21-001

Almotriptan (PNU-180638)

TRACKING LOG

DATE	DESCRIPTION
4/21/98	Tel. Contact: The NDA no. has been assigned to the almotriptan (PNU180638) NDA which is targeted for submission in December of this year. The NDA no. is 21-001.
12/15/99	Tel. Contact: FDA stated that our Pediatric Waiver request is in the queue with the Division (with many others). They will let us know when it has been passed from the Division to the Pediatric Committee. They also gave me her request for Desk Copies of the NDA summary volumes (below).
12/17/99	Original Submission of NDA.
1/6/00	General Correspondence – Response to FDA Request
1/7/00	Tel Contact: I called FDA to ask when we might expect the letter from them , acknowledging FDA receipt of the AXERT(TM) Tablets NDA. The target user fee date is 10 months from receipt of NDA.
1/13/00	FAX to FDA – Response to FDA question: Acceptance testing of bulk drug.
1/13/00	Tel. Contact – FDA phoned to provide a "heads up" on the CMC portion of our application – Item 4 must be part of our file.
1/24/00	Tel. Contact – FDA Field Office in Baltimore, MD, called to request a copy of Item 4 (CMC) for the PAI at Atlantic Pharmaceutical Services.
1/24/00	Tel. Contact: FDA was contacted regarding CMC Amendment. Notified FDA that a copy of NDA Item 4 was sent to the Baltimore District Office. FDA informed me that NDA was logged in at the Agency on 12/20/99.
1/25/00	General Correspondence/Response to Chemistry Reviewer's Request of 1/13/00.
1/27/00	FAX to FDA – Notification of plant closing dates to facilitate planning for PAI.
1/31/00	Tel. Contact – FDA called re: review. FDA stated the application is fileable, however an interaction study with ketoconazole must be conducted and reported. Medical Reviewed commented that electronic portion looked very good.
2/1/00	Tel. Contact – Called FDA to follow-up on previous request for address, list of attendees. Discussed User Fee date, status of pediatric waiver request and timing.
2/2/00	Tel. Contact: DSI called today to request specific info that will allow them to begin planning of their clinical study site audits. Info was requested for sites M/31416/13 and 14.

DATE	DESCRIPTION
2/2/00	Tel. Contact – FDA called to schedule the PAI for Industrias Farmaceuticas Almirall Prodesfarma. Proposed dates are 22-24 May 2000.
2/3/00	General Correspondence – summary of info in NDA regarding manufacturing facilities.
2/4/00	Tel. Contact – *[reissuing for date of contact correction]* Consumer Safety Officer from the Division of Emergency and Investigational Operations, phoned to schedule the PAI for Industrias Farmaceuticas Almirall Prodesfarma. The proposed dates are 22 through 24 May 2000.
2/7/00	General Correspondence, Response to DSI Request
2/8/00	General Correspondence: Request for teleconference.
2/9/00	Tel. Contact: FDA was contacted to confirm the proposed dates for the PAI inspection. FDA will inform as to whether a PAI would be included.
2/10/00	Tel. Contact: FDA called with two requests for calculations to aid in his review of the AXERT NDA.
2/15/00	General Correspondence – Response to Reviewer's Request
2/17/00	Tel. Contact: Regarding request for a teleconference to discuss the ketoconazole interaction study.
2/23/00	Tel. Contact: regarding the status of the Agency's review of protocol summary and when a teleconference could be arranged.
2/25/00	General Correspondence – Response to Reviewer's Request of 1/31/00.
2/29/00	Tel. Contact: Confirmation of P&U participation in teleconference scheduled for 3/3/00.
3/3/00	Tel. Contact: Teleconference was held today (3/3) to discuss design of ketoconazole drug interaction study – the protocol is acceptable.
3/7/00	Tel. Contact: FDA indicated that they will inspect both the laboratory facilities at APF and the bulk API plant —documentation on both will be needed.
3/22/00	Tel. Contact: DSI left me a PhoneMail message indicating they would like to get the foreign clinical inspections underway. Learned that they would like to inspect the following two sites in Germany during the last two weeks in June (6/19-6/30/00) At the sites, they will need to have available the CRFs for Study CL13, and a translator. Requested the data listings for efficacy endpoints for these sites be sent (hard copy) within a week.
3/28/00	Tel. Contact: I contacted DSI, to notify her that one of the inspectors was not available during the last two weeks in June, but would be available the week of 12 June or the week of 10 July. They felt that the week of 12 June might be a possibility, but would have to verify whether it fit DSI's schedule. I asked if she knew who would be inspecting the sites in Germany, but she did not.
3/30/00	General Correspondence – Response to DSI Request
3/31/00	Tel. Contact: Informed FDA that the data listings for efficacy endpoints for the Kademann and Zintzsch sites had not been picked up by the courier yesterday.

DATE	DESCRIPTION
4/3/00	Tel. Contact: DSI left a phonemail message to confirm that the second and third weeks of June would be acceptable to the FDA for the inspection of the two clinical sites in Germany. She also specified that the inspector would spend a full week at each site.
4/5/00	Tel. Contact: FDA called to request five years' historical control data for assay, or historical control data during the most recent period for whatever time range is "reasonable." We will contact FDA with an estimate of when information will be available.
4/5/00	Tel. Contact: FDA changed request for CRFs from either two blank CRFs or completed CRFs for one patient from each site--to they would NOT need any CRFs at this time since she had previously stipulated that case report forms were to be available at the sites.
4/6/00	Tel. Contact: FDA was contacted regarding request (of 5 April) for historical control data for study report 655/39.
4/6/00	Tel. Contact: FDA left message regarding electronic versions of the study summaries, and if it would be possible to send him the summaries of all the studies electronically (not data or listings). With assistance from the Clinical Pharmacology Unit, Regulatory will download the required files and send to both the FDA Pharmacology Reviewer and the FDA archives.
4/6/00	Tel. Contact: Called FDA to reconfirm that the dates 12-16 June and 19-23 June are acceptable to the CL13 trial investigators in Germany.
4/7/00	Tel. Contact: FDA Clinical Pharmacology Reviewer, and PNU exchanged voice mail messages today. The end result is that he said an electronic version of the PK study synopses from Item 6, Volume 1, Pages 37-100 would be fine.
4/11/00	Tel. Contact: Pharmacology question regarding the vehicle used in the lymphocyte tests in study 655/39 was the same vehicle used in the historical controls.
4/12/00	Tel. Contact: Called FDA to address pharmacology questions.
4/12/00	Tel. Contact: Called FDA to notify that the electronic files (PK study synopses) were being shipped today.
4/12/00	General Correspondence – PK Study Synopses for Clinical Pharmacology Reviewer
4/12/00	Fax to FDA – Response to request for historical solvent control data for study 655/39.
4/13/00	General Correspondence – Timing of Safety Update
4/13/00	Tel. Contact: Alerting that an e-mail will be sent re: confirmation of the hotel reservation for in May for PAI inspection.
4/13/00	FAX from FDA: Request from FDA re: phase 1 studies and draft labeling in Word format.
4/18/00	Tel. Contact: Requested a teleconference to discuss the results of the chromosome aberration study that was discussed last wk.
4/21/00	**Amendment 001:** Revised Package Insert

DATE	DESCRIPTION
4/20/00	**Tel. Contact** – FDA left message re: request for a teleconference to discuss the chromosome aberration study results. Still checking on request. Does not think it will be needed. Pharmacology group will send us something in writing.
4/26/00	**Tel. Contact** – FDA will put their request in writing – several other issues discussed during this contact.
4/28/00	**Desk Copy** - PNU sending two copies of Item 1 and Item 3, one copy of Item 6 to Project Manager to aid in the joint biopharmaceutics team working on the NDA review.
4/28/00B	**Amendment No. 002** – SAS transport files with ECG data.
5/2/00	General Correspondence: Additional Copy of CD-Rom PK Study Synopses for Clinical Pharmacology (CD provided previously (4/12/00) to Clinical Pharmacology Reviewer).
5/2/00	**FDA letter received** on 5/16/00 referencing NDA of 12/20/99. FDA provided comments/request in review of Pharmacology section.
5/8/00	**Tel. Contact** – FDA contacted to confirm the number of copies of CMC amendment we will submit this week
5/10/00	**Amendment No. 003** - stability data - CMC
5/12/00	**Tel. Contact:** Contacted FDA to discuss Zintsch and Kademann inspections.
5/16/00	**FDA letter** from Maryla Guzewska, Chemistry Team Leader, requesting information re: drug substance deficiencies. Wants revised specs to reference USP/NF method/
5/16/00	**FDA letter received via fax** – FDA interested in reviewing all ECG data collected in the immediate post-dosing period (i.e. <24 hours).
5/18/00	**Fax to FDA** – providing Response to Information Request letter being sent out today.
5/18/00	Tel. Contact – P&U has sent FDA letter responding to their information request letter and also to request a teleconference.
5/22/00	**Amendment 004** Amended Study report and Corrected Database Programming.
5/23/00	Tel. Contact: to FDA to ask if they had any success in pulling together the Pharmacology folks for the requested teleconference, and to ask for an informal teleconference between our Clinical Pharmacologist and the Biopharmaceutics reviewer to discuss the FDA's request for electronic datasets containing additional ECG data. **Additional request from FDA Statisticians regarding carcinogenicity data:** We were asked by the FDA to explain the large number of unusable tissues in the rat carcinogenicity study (655/68), and then resubmit data for both mouse and rat studies following the electronic submission guidance document (there should be one dataset for each study, rather than three for each study). In addition, the trend test for tumors should be performed where appropriate.
5/23/00	Personal Contact message: the inspectors have ended their inspection of Almirall and Ranke today and have recommended approval of the PAI. No 483 observations were noted. Only one comment which will be addressed in the EIR.

DATE	DESCRIPTION
5/24/00	General Correspondence – Preliminary Results from Study 638-CNS-0059-012
5/24/00	Tel. Contact: A teleconference was held today to clarify the 16 May request for additional ECG data to be submitted in electronic format. The outcome of the discussion was that data for CL01, CL04, CL09 and CL27 would not need to be included in our response. Although maximum exposure levels seen in CL01N, CL16 and CL18 were low, the FDA would still like to see the data.
5/25/00	Tel. Contact: Lana Chen has arranged available dates 6/8/00 or 6/9/00 to speak with Dr. Stolzenberg and Dr. Fitzgerald about their request for a repeat of the human lymphocyte assay.
5/26/00	Tel. Contact: To clarify the FDA's request of 23 May regarding the carcinogenicity studies, we contacted one of FDA's preclinical statisticians (per Lana Chen's directions).
6/5/00	Tel. Contact: To further clarify the FDA's request of 23 May regarding the carcinogenicity studies (and at the suggestion of the FDA, the Preclinical Statistical Reviewer we spoke with last week), we contacted a second Preclinical Statistical Reviewer assigned to our NDA. FDA called back after conferring.
6/7/00	Tel. Contact: FDA was called to confirm the teleconference with the Pharmacology team tomorrow, to request an informal telecon update on the status of the FDA request for electronic ECG data, to confirm the format of the Safety Update report, and notify the FDA of the APF market introduction study. The Pharmacology telecon is scheduled for 9:00 Thursday, 8 June. FDA will check with the Chemistry Reviewer and Team Leader to see if a CMC telecon would be possible at 9:30 on 9 June.
6/8/00	Tel. Contact: Project Manager at Neuropharm, left a message on my PhoneMail. In it, she suggested alternate times for the two teleconferences we've requested-Pharmacology Reviewer and CMC Reviewer. She also confirmed that no information is needed at this time about the market introduction study in Spain, and that they will let us know at a later date when they are interested in receiving the information.
6/8/00	General Correspondence – example of printed foil for tablets.
6/8/00	FAX to FDA: Seeking clarification of questions posed in the 5/16/2000 Information Request Letter.
6/9/00	Fax from FDA, minutes of teleconf with FDA, performed the required genotoxicity tests and assumed that there was no evidence of genotoxicity in any of the four studies performed. They believe that the results obtained in two of these studies, the human lymphocyte and the mouse lymphoma assays. are equivocal.
6/9/00	Tel. Contact: A teleconference was held to clarify the rationale and proposed methodology for a repeat of the human lymphocyte/chromosome aberration study.
6/9/00	FAX from FDA: Minutes of 6/9/00 teleconference.

DATE	DESCRIPTION
6/13/00	FAX to FDA: Request for clarification of certain details pertaining to requested submission of electronic data. Information needed to assist in fulfilling FDA request.
6/14/00	**Amendment 005:** SAS transport files containing ECG interval measurements for Phase 1 studies.
6/15/00	**Amendment 006** Safety Update with Clinical SR a0077618, Protocol 6380CNS-0059-012.
6/20/00	**FDA Fax** responding to PNU IR Letter dated May 16, 2000. Fax consists of FDA CMC Comments/requests.
6/22/00	**FDA Fax** received and the Clinical team has received a copy and is evaluating the request for additional ECG data (raw QT intervals for 9 studies).
6/28/00	Tel. Contact: we left a message to acknowledge receipt of the 22 June 2000 fax (re-faxed to us today), which requested electronic datasets containing the raw QT intervals for nine studies. we would let them know when a target date has been set.
6/28/00	FAX from FDA retransmission of 6/22 fax.
6/28/00	**FDA FAX** received from the FDA statisticians responding to 6/13/00 fax from PNU. Regarding Covance questions on the rat and mouse tumor datasets. Additional note regarding question 9: P&U routinely places electronic datasets on CD-Rom for submission to the Agency archives. The Agency's fax has been forwarded to Covance via fax.
6/29/00	**Amendment 007** - Discussion of Genetic Toxicology of Almotriptan.
6/30/00	**Amendment 008** – Response to Information Request Letter – CMC.
6/30/00	Tel. Contact: Informed FDA that our response to the CMC Reviewer's request had been sent today, and that the DMF amendment was submitted by our license partners today.
6/30/00	Tel. Contact: Confirmed that the method preferred be used for measuring for toxicity was indeed, the way we asked the CR"O to calculate the data – using RTG rather than RS.
7/5/00	General Correspondence/Response to 483: Clinical Investigator Inspection Package: Dr. Ingo Zintsch
7/6/00	Tel. Contact: We contacted FDA to inform them that the response to the 483 had been sent yesterday to her attention, and asked if we could set up a time to talk with them tomorrow. They advised that they were not in a position to discuss anything since they haven'tt yet even received the EIR. They declined to plan a future date, and seemed to be recommending that we wait until we hear from the review division.
7/7/00	Tel. Contact: The Biopharm Review team called to request a Desk Copy of all ECG data files that were sent to the Medical Reviewer. In addition they are requesting to receive the systolic and diastolic blood pressure measurement data.
7/11/00	Tel. Contact: I asked FDA if there had been any response to our June 29 request to either reopen discussions about the genetic toxicology of almotriptan with the Pharmacology Reviewer, or to obtain an opinion from the full CAC. They said they would check and get back to me as soon as she finds out—or I could check back with her in a day or so.

DATE	DESCRIPTION
7/11/00	Tel. Contact: After a conversation with, Covance, I contacted FDA to request a teleconference. The teleconference is set for 11:00 Thursday, 13 July 2000.
7/11/00	**Amendment 009** - Response to Medical Reviewer's Request.
7/12/00	Tel. Contact: I left a voice mail message for Lana Chen. I inquired again about the status of our June 29 General Correspondence containing a discussion of the genetic toxicology of almotriptan.
7/12/00	Tel. Contact: I spoke with FDA about the status of our June 29 General Correspondence. The issues will be discussed at the Executive Carcinogenicity Assessment Committee meeting on July 18. If the Exec CAC's recommendation is straightforward, FDA said they would call me. Final minutes are faxed from the CAC to sponsors–typically within a couple weeks after the meeting.
7/13/00	General Correspondence, Clinical Investigator Inspection: Dr. Barbara Kademann
7/13/00	Tel. Contact: FDA was contacted to further clarify FDA answers to Items 4, 5a and 6 on the 28 June 2000 FDA fax.
7/14/00	FAX to FDA asking for confirmation for the points regarding subject studies 655/67(mouse) and 655/68(rat).
7/18/00	Desk Copy of Amendments 002, 005, 009; 3 CD-Roms containing ECG data.
7/19/00	Tel. Contact: FDA left me a PhoneMail message this morning, to ask if we had a timeline for re-submission of the carcinogenicity datafiles, as requested by the FDA preclinical statisticians on 28 June. When I returned their call, I told them that the datafiles from the mouse study would be submitted early to mid-week, the week of 7 August.
7/19/00	Tel. Contact:FDA, called to confirm that BP data is requested for all Phase 1 and 2 studies, as listed on the table detailing ECG monitoring that was provided in an earlier FDA fax (dated 16 May 2000). I told them we were working on those datafiles and that I would let him know when we expected to submit them.
7/24/00	Tel. Contact: PNU called FDA Preclinical Statistician, to verify receipt of 14 July fax requesting confirmation of the electronic submission requirements for tumor coding. FDA indicated that she had received the fax. Further, she stated that an internal FDA meeting is scheduled for Wednesday, 26 July at which this issue will be discussed. After that an answer will be faxed.
7/26/00	**Amendment No. 010** – DMF 12475 Amendment Included by Reference
7/27/00	Telephone Contact: We left a message, FDA Preclinical Statistician, and explained that if we could receive an answer today to our 14 July fax, we could still possibly meet the targeted date for resubmission (week of 7 August) of the mouse carcinogenicity datasets. I told her that the timing of the resubmission of the rat datasets also hinged on the availability of her response.

DATE	DESCRIPTION
7/28/00	Tel. Contact FDA, I left a voicemail message (marked "urgent"), asking that they check on the status of the response to our 14 July fax, requesting an update (if available) on the outcome of the 18 July Exec. CAC meeting, and explaining that the timing of the resubmission of electronic datasets from the rat and mouse carcinogenicity depend on how soon we can received an answer. FDA called back-they will contact and convey the importance of their answer, then call us back with the status. They will check as to whether they can give us an update on the outcome of the Exec. CAC committee prior to the issuance of the minutes (approximately 30 days after the meeting).
7/28/00	Tel. Contact from FDA, (Project Manager) called again, this time with (Chemistry Reviewer) in their office. Because the Excel file (within Amendment 008-CMC data submitted 30 June) containing the regression analysis is not archivable at the FDA, they need for us to submit that information in either paper or SAS transport form. I suggested that we include the paper copy of the regression analysis with the other outstanding CMC information, which we anticipated submitting around the end of August. They agreed that it could be combined with another submission.
7/28/00	Telephone Cont. and (2) FDA Faxes to FDA, Preclinical Statistician, will fax us the response to our 14 July request, concerning tumor coding in the carcinogenicity data. They asked that we contact them if we feel the response doesn't seem to cover all possible eventualities.
8/28/00	FDA Fax of 7/18/00 CAC Meeting Minutes
8/4/00	**Amendment 011:** General Correspondence – Response to concerns raised on mouse protein binding and metabolism.
8/4/00	Tel. Contact: The biopharmaceutics reviewer asked for information pertaining to the food effect study (M.31416.04R).
8/4/00	Tel. Contact: FDA called to request PK data electronically for the ketoconazole interaction study—the same as was provided for other PK studies.
8/4/00	Tel. Contact: FDA called to inquire about the status of the mouse lymphoma and human lymphocyte studies.
8/4/00	Tel. Contact: Contacted FDA to respond to the Biopharmaceutics Reviewer.
8/4/00	FAX to FDA: Response to Executive CAC Minutes (July 18, 2000)
8/7/00	**Amendment 012:** Response to Preclinical Statistical Reviewer Request
8/7/00-2	**Amendment 013:** Response to Biopharmaceutics Reviewer Request
8/7/00	Tel. Contact: FDA called to inform us that he is not planning on scheduling the full CAC committee meeting we requested in our fax correspondence last week.
8/7/00	Tel. Contact: : FDA inquired about the genotox studies, asking when information would be available for FDA review.
8/9/00	Tel. Contact: Contacted FDA to explain that we would be able to send interim data as it becomes available.

DATE	DESCRIPTION
8/9/00	Tel. Contact: Covered with FDA request from Medical Reviewer, genotox studies, Clinical Reviewers comments, DSI Inspection Report and Timlines/comments on potential action.
8/9/00	Tel. Contact: Contacted FDA to inform that we would be sending the electronic data for the ketoconazole/almotriptan interaction study by August 14.
8/10/00	Tel. Contact: FDA called to ask which QTc correction method was used in the analysis of the long-term dog study (655/69).
8/10/00	Tel. Contact: Called FDA to confirm that the QTc correction method used in the analysis of the long-term dog study (655/69 was, indeed, Bazett's).
8/10/00	Tel. Contact: Contacted FDA to question whether in addition to splitting the datasets for CHEMCL25 and HEMACL25, he would like us to also split the two other oversized files. FDA confirmed they would appreciate the LABC0011 and CHEMCL14 datasets being split. Notified them the files would be corrected by the end of the week.
8/14/00	**Amendment No. 014** Response to Preclinical Statistical Reviewer Request.
8/14/00a	**Amendment No. 015** Response to Biopharmaceutics Reviewer Request.
8/14/00b	**Amendment No. 016** Response to Medical Reviewer Request.
8/21/00	Tel. Contact: FDA Project Manager called to ask whether the Executive CAC had faxed the Addendum/Revision to the 18 July minutes. He had received the revised minutes late in the day on 17 August and said he would fax them to PNU today (see next entry).
8/21/00	FDA FAX: Revised Executive CAC Recommendations and Conclusions: Based on this information identified by the sponsor from their original submission, the Committee now agrees that the doses were adequate, provided that there is no evidence of genotoxicity in the currently ongoing genotoxicity studies.
8/24/00	**Tele Contact**: A lot of adverse events have been read into data that aren't really there. FDA suggests we rewrite the sections pertaining to this issue specifically the cardiovascular system-dogs in the Pharm. Section. P&U will submit summary by end of next week.
8/24/00	**Tele. Contact**: FDA called for clarification of the results reported from the protein binding studies. P&U responded to questions regarding protein binding methodologies (ultrafiltration and equilibrium dialysis).
8/25/00	**Amendment 017** - Response to Chemistry Reviewer Request.
8/29/00	**Amendment 018** - Response to Chemistry Reviewer Request.
9/5/00	**Amendment 019** – Response to Preclinical Pharmacology Reviewer Request.
9/5/00	Electronic copy of Amendment 019 sent to FDA (Nighswander).
9/12/00	Tel. Contact – FDA phoned asking about the timeline for submitting the mouse lymphoma study results.
9/13/00	Tel. Contact – FDA would prefer receiving a WORD file when receiving documents electronically.

DATE	DESCRIPTION
9/14/00	E-mail – we were informed on 5 October between the counterpart from APF and FDA who conducted the pre-approval inspection at APF facilities in Barcelona in May 2000. No FDA-483 was indicated they have not yet finished their report.
9/14/00	Tel. Contact – FDA contacted to ask about acceptability of the imprint code change to the 6.25 mg tablet and to generally obtain any insight into the progress of the Agency's review.
9/18/00	Tel. Contact: Ms. Lana Chen and I discussed the status of the NDA review. The Agency is keen to have an action in October, but at this point, it looks like the pending preclinical report would cause the action to be "approvable" rather than an approval. It may also cause other parts of the review to proceed more slowly.
9/19/00	Tel. Contact: Ms. Lana Chen left me a message in reply to my question regarding the acceptability of the imprint code. She said it seems there are some problems with what we have proposed and that they couldn't really guarantee that it would be acceptable to the Agency. I have asked her for additional details.
9/19/00	E:Mail to the FDA: Asking Dr. Heimann's advice on a minor change being considered for the labeling of AXERT Tablets. Due to the merger, discussions are taking place regarding a possible change in the NDC number and company signature to be used on the labeling. Specifically, a Searle NDC would be used instead of a Pharmacia & Upjohn NDC. In addition, a Searle company name or signature would appear wherever there is currently a P&U name or signature.
9/19/00	E:Mail to the FDA: Additional questions/comments regarding the reviewers possibility of not being ready to go straight to approval. Is there a way you can provide us more details about their objections? Copies of their reviews would certainly be welcome (even if they were FOIable). However, if the reviewers aren't comfortable with that, or things are too much "up in the air" we would still appreciate information verbally from you about the issues being discussed.
9/19/00	E-mail to the FDA to follow-up on a phone discussion to ask if they could either provide copies of the reviewer comments or at least read them to me over the phone. I also asked whether the problem with the imprint was the color, the symbol or something else.
9/19/00	E:Mail Contact: Requested that Ms. Chen ask Dr. Heimann for advice on the possible switch to a Searle NDC number/signature on the AXERT labeling, currently under consideration at P&U.
9/22/00	**Amendment 20** - Response to Preclinical Pharmacology Reviewer Request
9/22/00	E-mail to the FDA to provide an advance electronic copy of Amendment 020 (which contains an interim report from the mouse lymphoma study).
9/22/00	E-mail from the FDA to thank me for the electronic copy of the interim mouse lymphoma data. He stated that his review will be finalized after receipt of the final audited report.
9/27/00	**Amendment 021** - Response to Preclinical Pharmacology Reviewer Request

DATE	DESCRIPTION
9/27/00	E:mail Contact: An e-mail was sent to Dr. Stolzenberg to provide an answer to his question regarding the mouse lymphoma study. I also informed him that (since the secure e-mail system wasn't operational) a floppy disk would be sent today via overnight express mail, which contains the electronic version of the summary of cardiovascular affects of almotriptan in dogs (in addition to the hard copy in Amendment 021).
9/27/00	Tel. Contact: I called to notify Dr. Stolzenberg that the summary of the cardiovascular effects of almotriptan in dogs was being sent to him today. He asked a question regarding the preliminary data from the mouse lymphoma study– what the incubation periods were for each of the 3 experiments without S-9. I told him I would obtain that information and call him back.
9/29/00	E-Mail from FDA, acknowledge receipt of the rewritten summary, also they sent a separate e-mail simply stating thank-you to the answer to their question about incubation periods.
9/29/00	Tel. Contact: FDA called regarding the outcome of the group meeting, the final report was considered critical and they would not be receiving any add'l deficiency letters prior to the action dated. Their opinion that this would not be the one and only review cycle.
10/3/00	Tel. Contact: We learned more information from the FDA, about the status of the review. We informed them that audited data from the last portion of the mouse lymphoma study would be sent both electronic and hard copy.
10/3/00	**Amendment 022**, Response to Preclinical Pharmacology Reviewer Request
10/4/00	E-Mail from FDA, asking for clarification on the talbels containing the pH readings taken during the study. We sent FDA a e-mail to confirm receipt of their inquiry concerning the study results and assured them we would obtain an answer asap.
10/5/00	FDA sent e-mail to clarify that they would prefer a verbal response to their questions. We left a voice mail to answer they inquiry all of the assumptions be stated in his e-mail were correct.
10/6/00	E-mail from FDA, some preliminary comments and requests after reviewing the audited data from Amendment 022, which contained results from the study of effects of pH on almotriptan in the study. Our Toxicology department is working with the contract lab to formulate a response.
10/9/00	**Amendment 023**, Response to Preclinical Pharmacology Reviewer Request, Study Report 0624-2000
10/10/00	E-mail sent to FDA, acknowledging receipt of their 6 October inquires and to provide them with an electronic copy of Amendment 023.
10/10/00 (a)	Tel. Contact: FDA was contacted and informed that they would receive Amendment 023 today.
10/10/00 (b)	Tel. Contact: FDA was contacted and informed what electronic files were available containing the final study report for the mouse lymphoma assay.

DATE	DESCRIPTION
10/11/00	Tel. Contact: FDA returned our call confirming receipt of the 10th October e-mail and they answered our questions regarding handling of the action letter on 20 October, they will handle notifying us of the action.
10/12/00	E-mail to FDA, to follow up on a phone conversation, we attached a WORD version of the text of the final audited study report submitted 9 October, Amendment 023.
10/13/00	**Amendment 024:** Response to Preclinical Pharmacology Reviewer Request
10/13/00	Fax to FDA: Copy of Amendment 024.
10/13/00	Fax to FDA: Informed of the outcome of the repeated tox studies that were requested by FDA.
10/16/00	Tel. Contact: FDA will fax a copy of an extension letter — extending the primary review by 3 months – to 20 January, 2001. The Agency is considering the 5 September 2000 submission (human lymphocyte final report) to be a major amendment; still doubting that the action in January will be "approval," and stated they are moving to an "approvable".
10/16/00	FDA letter received 10/24/00: Re extension of user fee goal date.
10/16/00	Fax from FDA: Faxed copy of extension letter dated 10/16/00.
10/17/00	Tel. Contact: FDA Chen returned our call regarding further details on the status of the NDA. The FDA review team was targeting the 10-month date, therefore, all the reviews except for the Preclinical review are at the Division Director level.
10/24/00	Tel. Contact: FDA called with the following question in reference to the mouse lymphoma study. Was colony size counted in any of the almotriptan treated cultures? If so, FDA would appreciate seeing the results.
10/25/00	Tel. Contact: A telephone message was left for FDA from Toxicology for 10/24/00 request.
11/2/00	General Correspondence: Request for outstanding issues.
11/28/00	Tel. Contact: I left a message for Dr. Katz asking him to contact me regarding my letter of 2 November.
11/29/00	Tel. Contact: Ms. Lana Chen called to say we have received all the information we were going to receive prior to the action letter and that the file is still actively under review, with a target of 20 January.
12/4/00	Tel. Contact: A teleconference was held today with Ms. Chen and Dr. Katz (Division Director, Neuropharm). The data from the repeated genotoxicity studies has been reviewed by the Agency. The results are still considered questionable and therefore the issues were taken to the Executive Carcinogenicity Assessment Committee.
12/5/00 (a)	Tel. Contact: As FDA has not yet sent the fax detailing the Review Divisions questions for the Full CAC, a voice mail message was left today. I asked questions regarding the logistics of the meeting, and for FDA to call back.

DATE	DESCRIPTION
12/5/00 (b)	Tel. Contact: a second message was left with the FDA asking if they could locate the fax which details the questions to be addressed by the Full CAC next week; I asked to please fax it to us by the end of the day today.
12/6/00	Tel. Contact: FDA left a voice mail in response to my questions pertaining to next week's Full CAC meeting. In subsequent calls, we discussed additional details: The meeting will take place Wednesday 13 December at 1:00 p.m. in the Woodmont II building conference room F, on the 5th floor.
12/6/00	FDA called to say they had some questions regarding the chemistry response, they explained that they need additional information on the chemistry comments 5 and 8 of the Approvable Letter, and on the Methods Validation package.
12/7/00	Tel. Contact: Called FDA to ask about the status of the questions for the CAC and find out a bit more about the logistics of the meeting. They are very aware of our need for the list of questions for the CAC and assured me that it was Drs. Fitzgerald and Stolzenberg's top priority. I asked if we could receive a copy of the Agency's presentation; they said they have been advised not to share any pieces of the review prior to release of the action letter.
12/8/00	Tel. Contact: I left a message this morning for Mr. Robbin Nighswander- - again inquiring about the status of the questions for the CAC.
12/8/00	Tel. Contact – Request that FDA fax the latest Exec. CAC meeting minutes to P&U and to set up a tel. Conf.
12/8/00	Tel. Contact – FDA returned call with two questions. If question 1 gets a "no" from the CAC, then we would be asked what further studies we would propose. P&U will make a 30-minute presentation first, then FDA will present followed by Q&A.
12/8/00	FDA letter received via fax providing two questions for P&U
12/11/00	Tel. Contact – A brief tel. Conf. Was held with FDA to discuss their concerns with the repeated genetic toxicology studies with almotriptan.
12/11/00	FDA letter received via fax re: Executive CAC Minutes attached.
12/13/00	Meeting with FDA – presentation given to the FDA Full Carcinogenicity Assessment Committee.
12/15/00	**Amendment 025:** Full CAC pre-meeting briefing package.
12/20/00	Tel. Contact – FDA is still reviewing comments from the group, will be a few days before finalized. Possible action letter by the end of this month.
12/21/00	FDA letter received via facsimile providing approvable letter and labeling of 12/20/00.
12/28/00	**General Correspondence** - Intention to Amend NDA
1/2/01	Tel. Contact: Request for teleconference with Chemistry and Clinical reviewers and copy of CAC meeting minutes.
1/3/01	FAX to FDA: Questions for Chemistry and Clinical reviewers.
1/3/01	Fax from FDA: Full CAC minutes.

DATE	DESCRIPTION
1/4/01	Tel. Contact: FDA and P&U discussed Chemistry questions of 1/3/01 fax will be answered by FDA soon. Review of clinical study to prepare for teleconference on 1/17/01. Request for translateions of Spanish labeling.
1/5/01	**General Correspondence** – Chemistry, Proposed Tablet Imprint Codes
1/5/01	Tel. Contact: FDA called Pharmacia this morning to clarify the request for an outlier analysis of blood pressure data (please see details below). FDA stated that hoped to provide feedback on points 1-3 of the Clinical Section of the Approvable Letter via fax next Monday or Tuesday.
1/5/01	Fax to FDA: Fax of letter and attachments (imprint.pdf) that were submitted to the FDA today (5 January). In addition, an advance copy was faxed (see 05jan01f.doc) to the Chemistry Reviewer, for her review--with the hopes that she could comment on the proposed imprint scheme when she responds to our earlier fax (dated 3 January). I was told we can expect the response fax from Dr. Heimann "early next week".
1/9/01	FDA Fax: Please note that it contains the FDA response to the Clinical (not CMC) questions we posed via fax on 3 January 2001.
1/11/01	Tel. Contact: As a follow-up to the faxed response from the Chemistry Reviewer, I asked FDA when we would know 1) if the imprint scheme was acceptable, and 2) how soon after our complete response letter is received at the Agency would it be classified as a Class 1 (2 month) or Class 2 (6 month) review. Answers: 1) the acceptability of the imprint scheme would be determined during the review and 2) after receipt of our complete response letter, there is no time limit for the Agency to respond to us with the class of the resubmission.
1/11/01	FDA Fax: Contains responses to our CMC questions posed in our faxes dated 3 January and 5 January 2001.
1/23/01	**Amendment No. 026** – Complete Response to Approvable Letter
1/26/01	FAX to FDA containing the corrected page 5 of the Complete Response Letter (Amendment No. 026)
1/29/01	**Amendment No. 027** – Correction to previous submission
2/13/01	FAX to FDA: Seeking clarification concerning follow-up questions to our responses to the approval letter.
2/14/01	Tel. Contact: A teleconference was held today with FDA to discuss the remaining information needed to complete their review of the NDA.
2/20/01	Tel. Contact The Director of Quality Assurance at Industrías Farmacéuticas Almirall Prodesfarma (IFAPF) contacted the FDA Investigator who led the PAI of RANKE Química and IFAPF. The purpose of the call was to clarify further the situation regarding the outstanding inspection report for the PAI at IFAPF in Barcelona in May. In addition, they discussed the transfer of SOPs from the R&D Centre to the Pharmaceutical Plant Quality Control.
3/5/01	**Amendment No. 028** – Response to CMC Questions
3/13/01	**Amendment No. 029** Response to CMC Reviewer's Request.

DATE	DESCRIPTION
3/7/01	Fax to FDA notifying FDA that Amendment 028 did not include a Field Copy Statement. This statement was included in this fax.
3/19/01	Tel. Contact: FDA Project Manager was contacted to find out if the Chemistry Reviewer had reached a decision pertaining to the acceptability of the imprint. Reviewer will check with the Chemistry Reviewer on the status of this issue. In addition, Reviewer will check on status of imprint scheme sent to OPDRA, and if not, when it is sent. Reviewer acknowledged that we have a short time line and that if changes were required, it would take additional time.
3/20/01	Tel. Contact: The information in a PhoneMail message left this morning by the FDA Project Manager substantially reduces the risk to print 12.5 mg tablets with the stylized A, although the 100% acceptability will not be known until an action letter is received.
3/20/01	FDA Fax: Teleconference minutes of February 14, 2001.
3/21/01	Tel. Contact: A letter was issued from the FDA yesterday classifying our March 6, 2001 Resubmission as "Class I." This means the Agency's target action date is May 4, 2001.
3/27/01	Letter received from FDA acknowledging receipt of 1/23/01 submission – user fee goal date is 5/6/01.
3/28/01	**General Correspondence** – Proposed Pediatric Study Request and Pediatric Drug Development Plan
4/4/01	Tel. Contact: An FDA error in calculation of the primary user fee goal date as it appeared in the 20 March acknowledgment letter was corrected verbally—rather than a target of 6 May, the target for an FDA action letter is Monday, 7 May 2001.The action letter may contain a reply to our Proposed Pediatric Study Plan, or a response may be sent separately. If labeling negotiations are needed, they could occur within the next few weeks.
4/5/01	Tel. Contact: FDA called to alert me to a secure e-mail that she had sent. The Agency requests a rationale for proposing dosage reduction in the renally impaired and not for patients who are coadministered ketoconazole.
4/9/01	**Amendment No. 030** - Response to Biopharmaceutical Reviewer's Request
4/17/01	Tel. Contact to the FDA, they were notified that we are reviewing the agency's draft approved insert, our company's senior management must approve our recommendation before we can respond to the FDA, we requested the agency's detailed reply to our pediatric study plan be addressed in a communication separate from the action letter, the latter would be a public document under the FOI Act.
4/19/01	Telephone Contact from FDA, they requested a copy of a page that was missing from the method validation for related substances of the API.
4/19/01	Fax to FDA, correct replacement page for volume 2 page 70 sent, for the subject amendment page 232 of Almirall Prodesfarma S.A. DMF Type II, January 2001 version
4/19/00	Telephone contact from FDA, they asked that we provide an electronic copy of the draft PI to Dr. Oliva as well as to them.

4/20/01	**Amendment No. 031** – Correction to previous submission (CMC Methods Validation Package).
4/20/01	Tel Contact from the FDA, Philadelphia labs, confirmed receipt of the fax sent 4/19/01, they need answer to some quesitons before they write the letter requesting table samples, we told them that the answers needed to come from our license partners (APF) in Spain, we wouldn't have answers until Monday, April 23.
4/24/01	E:mail contact, an advance electronic copy of amendment no. 032 was sent via e-mail to the agency
4/25/01	**Amendment No. 032** – Acceptance of FDA's Draft Approval Package Insert
4/26/01	Tel. Contact from FDA, changes have been made to the insert by DDMAC, minor changes were made to the precautions section in paragraphs on mutagenecity and impairment of fertility.
4/26/01	Tel Contact to FDA, in response to our inquiry they confirmed that the rationale we presented in our 23 January complete response had been considered when they made the changes we received today. They said in order for the action letter to be issued by the target date it must leave the division tomorrow.
4/26/01	Tel Contact to FDA, we left a voice mail asking to explain what was driving the addition of two of the paragraphs in the patient information section of the revised insert we received earlier today
4/27/01	Tel. Contact: A teleconference was held with the FDA to discuss the changes presented by the Agency yesterday. The FDA agreed with us to revise the two sentences that we considered objectionable. Later today, the Division will forward the action letter and package insert to Dr. Temple for his signature, for issuance by 7 May.
4/30/01	**Amendment No. 033** – CMC – Methods Validation/Correction to SOPS
5/4/01	Tel. Contact: Labeling negotiations are on-going. We received some minor changes to the Clinical Pharmacology, Precautions and Adverse Events sections from the Agency. We were alerted to a fax that was being sent regarding the Methods Validation package.
5/4/01	FAX from FDA: Request for Methods Validation package.
5/4/01	Tel. Contact: After two rounds of labeling negotiations today, Neuropharm has sent the insert text to Dr. Temple for his signature. The action letter will not issue until Monday, 7 May, 2001.
5/4/01	Tel. Contact: An e-mail was sent 4 May to FDA to follow up on a voice mail message left for her earlier in the day regarding FDA changes to the Package Insert text. The e-mail stated that Pharmacia & Upjohn is in agreement with the changes to the Precautions subsections "Binding to Melanin-Containing Tissues" and "Corneal Opacities", and with the previous changes to the Clinical Pharmacology, "Precautions" and "Adverse Events" sections.

5/7/01	Tel. Contact: Received FDA's approval for AXERT Tablets (almotriptan malate tablets) for the acute treatment of migraine with or without aura in adults.
5/7/01	**General Correspondence** – Change of Ownership of an Application
5/7/01	FDA Letter dated 5/7/01 and received 5/16/01. Sample materials received in good condition and placed in storage as indicated on the packaging.
5/8/01	**General Correspondence** -- Change in Ownership of Application
5/14/01	**General Correspondence** - FPL for Approved NDA 21-001 (CD-ROM)